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Proposed Registration Decision PRD2017-10

Tioxazafen and MON 102133 SC Nematicide Seed Treatment

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Table of Contents

Overview 1
Proposed Registration Decision for Tioxazafen 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is Tioxazafen? 2
Health Considerations 2
Environmental Considerations 4
Value Considerations 5
Measures to Minimize Risk 5
Next Steps 6
Other Information 6
Science Evaluation 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product 7
1.3 Directions for Use 8
1.4 Mode of Action 9
2.0 Methods of Analysis 9
2.1 Methods for Analysis of the Active Ingredient 9
2.2 Method for Formulation Analysis 9
2.3 Methods for Residue Analysis 9
3.0 Impact on Human and Animal Health 10
3.1 Toxicology Summary 10
3.1.1 *Pest Control Products Act* Hazard Characterization 15
3.2 Acute Reference Dose (ARfD) 15
3.3 Acceptable Daily Intake (ADI) 15
3.4 Occupational Risk Assessment 16
3.4.1 Toxicological Endpoints 16
3.4.2 Occupational Exposure and Risk 17
3.4.3 Residential Exposure and Risk Assessment 22
3.5 Dietary Exposure Assessment 22
3.5.1 Residues in Drinking Water 22
3.5.2 Residues in Plant and Animal Foodstuffs 23
3.5.3 Dietary Risk Assessment 24
3.5.4 Aggregate Exposure and Risk 25
3.5.5 Maximum Residue Limits 25
4.0 Impact on the Environment 25
4.1 Fate and Behaviour in the Environment 25
4.2 Environmental Risk Characterization 27
4.2.1 Risk to Terrestrial Organisms 28
4.2.2 Risk to Aquatic Organisms 31
5.0 Value 33
5.1 Consideration of Benefits 33
5.2 Effectiveness Against Pests 33
5.3 Non-Safety Adverse Effects 33
5.4 Supported Uses 33
6.0 Pest Control Product Policy Considerations 34
6.1 Toxic Substances Management Policy Considerations 34
6.2 Formulants and Contaminants of Health or Environmental Concern 34
7.0 Summary 35
7.1 Human Health and Safety 35
7.2 Environmental Risk 36
7.3 Value 36
8.0 Proposed Regulatory Decision 36
List of Abbreviations 37
Appendix I Tables and Figures 39
Table 1 Residue Analysis (Soil and Water) 39
Table 2 Toxicity Profile of MON 102133 SC Nematicide Seed Treatment, containing TIOXAZAFEN 39
Table 3 Toxicity Profile of Technical TIOXAZAFEN 41
Table 4 Toxicity Profile of Metabolite MON 102130 (photolyte of TIOXAZAFEN) 47
Table 5 Toxicology Endpoints for Use in Health Risk Assessment for TIOXAZAFEN 48
Table 6 Integrated Food Residue Chemistry Summary 49
Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment 75
Table 8 Route of Transformation and Transformation Products in Environmental Fate Studies 76
Table 9 Fate and behaviour in the terrestrial and aquatic environments 77
Table 10 Toxicity to non-target terrestrial species 80
Table 11 Toxicity to non-target Aquatic species 81
Table 12 Risk assessment of oral exposure to pollen and nectar from seed treatment of tioxazafen (MON102133 Nematicide SC Seed Treatment) to honey bees (*Apis mellifera*) 82
Table 13 EEC and risk to non-target terrestrial organisms except bees, birds and mammals 82
Table 14 Risk to birds and mammal from the use of treated soybeans 83
Table 15 Risk to birds and mammal from the use of treated corn seeds 83
Table 16 Major surface water model inputs for Level 1 assessment of tioxazafen 84
Table 17 Modelled Expected environmental concentrations (EECs) and risk quotients (RQs) for aquatic organisms 84
Table 18 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria 85
Table 19 Registered Alternatives in Canada for Use as Seed Treatments as of October 2015 86
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications 87
Table 1 Differences Between MRLs in Canada and in Other Jurisdictions 87
References 89

Proposed Registration Decision - PRD2017-10

Overview

Proposed Registration Decision for Tioxazafen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of MON 102100 Technical and MON 102133 SC Nematicide Seed Treatment, containing the technical grade active ingredient tioxazafen, to suppress certain soil-inhabiting nematodes in field corn and soybeans.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of MON 102100 Technical and MON 102133 SC Nematicide Seed Treatment.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on tioxazafen, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on tioxazafen, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Tioxazafen?

Tioxazafen is a new active ingredient for nematode management in field corn and soybean. It has a mode of action that causes gene mutation in targeted nematodes. Tioxazafen provides broad spectrum suppression of nematodes when used as a seed treatment on field corn and soybean.

Health Considerations

Can Approved Uses of Tioxazafen Affect Human Health?

MON102133 SC Nematicide Seed Treatment, containing Tioxazafen, is unlikely to affect your health when used according to label directions.

Potential exposure to tioxazafen may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, the technical grade active ingredient tioxazafen was of low acute toxicity via the oral, dermal and inhalation routes of exposure. Tioxazafen was minimally irritating to the eyes and non-irritating to the skin, and did not cause an allergic skin reaction. Consequently, no acute hazard labelling is required for the technical grade active ingredient.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The end-use product, MON102133 SC Nematicide Seed Treatment, was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was slightly irritating to the skin, not irritating to the eyes, and did not cause an allergic skin reaction. Consequently, no acute hazard labelling is required for this end-use product.

Short- and long-term (lifetime) animal toxicity tests, and information from the published scientific literature were assessed for the potential of tioxazafen to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment were effects on body weight and the adrenal gland, as well as increased numbers of normal cells at the site of contact following dermal and inhalation exposure. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most tioxazafen relative to body weight, are expected to be exposed to less than 3% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from tioxazafen is not of health concern for all population subgroups.

The lifetime cancer risk from the use of tioxazafen on field corn, soybean and imported cotton is not of health concern.

Aggregate acute dietary intake estimates (food plus drinking water) for the general population and all population subgroups were less than 1% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was children 1-2 years old.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States including representative Canadian growing regions using tioxazafen on field corn, soybean and cotton are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this consultation document.

Occupational Risks From Handling MON 102133 SC Nematicide Seed Treatment

Occupational risks are not of concern when MON 102133 SC Nematicide Seed Treatment is used according to the label directions, which include protective measures.

Workers treating seed with MON 102133 SC Nematicide Seed Treatment in commercial facilities or by commercial mobile systems, and workers planting treated seed can come into direct contact with tioxazafen residues on the skin and through inhalation. Therefore, the label specifies that workers treating and handling treated seed must wear the following personal protective equipment. In commercial seed treatment facilities and for commercial mobile treaters, workers mixing and loading must wear a long-sleeved shirt, long pants and chemical-resistant gloves; cleaners must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves; and baggers, sewers, stackers, and workers performing other activities not involving direct contact with treated seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves. Closed transfer mixing and loading is required for treating seed in commercial seed treatment facilities and for mobile treaters. Closed cab tractors are required when planting treated seed, and planters must wear a work jacket over a long-sleeved shirt, long pants and chemical-resistant gloves for loading and sowing of treated seed. Taking into consideration these label statements and the expectation of the exposure period for handlers and workers, the health risk to these individuals is not of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Tioxazafen Is Introduced into the Environment?

Tioxazafen is not expected to pose risks of concern when used according label directions. Tioxazafen is not expected to pose risks to aquatic organisms, beneficial insects, earthworms or terrestrial plants. Tioxazafen can pose a risk to non-target birds and small mammals if they consume enough treated seeds; therefore, statements on the product labels are required to inform users of potential risks and indicate that all treated seeds must be removed or incorporated into soil. When label directions are followed, the risk is considered acceptable.

Tioxazafen can enter the environment when treated seeds are planted.

In the terrestrial environment, tioxazafen is slightly persistent to persistent in soil and can carry over to the following growing season in certain types of soil. It breaks down in the presence of microbes to form various substances that are not expected to form in large amounts in the environment. Tioxazafen binds tightly to soil particles and remains in the top soil layers: it has a low potential for moving through soil.

Tioxazafen can reach the aquatic environment when transported along with eroded soil in runoff after rainfall. Once in the aquatic environment, it does not break down in the presence of sunlight but does break down in the presence of microbes and can bind to sediments.

It can form various substances, but these are not expected to reach levels that could be of concern to the environment when used as a seed treatment. Tioxazafen has the potential to accumulate at low levels in plant and animal tissues, but not to levels that would cause concern.

Tioxazafen is not expected to move in air and be transported long distances from where it was applied.

When tioxazafen is used according to the label directions, effects on plants, bees and aquatic organisms are not expected. Eating treated seed may, however, result in effects on birds and small mammals. For smaller birds, eating a small number of seeds could result in toxic effects. In order to reduce the risks to birds and small mammals, users of treated seed are required to bury or remove any spilled or exposed treated seed from the soil surface to help reduce exposure.

Value Considerations

What Is the Value of MON 102133 SC Nematicide Seed Treatment

Tioxazafen, the active ingredient in MON 102133 SC Nematicide Seed Treatment, suppresses certain soil-inhabiting nematodes in field corn and soybean.

MON 102133 SC Nematicide Seed Treatment, containing tioxazafen, has been demonstrated to be effective against certain soil-inhabiting nematodes in field corn and soybean including economically important ones such as the soybean cyst nematode. It suppresses various nematodes during the seedling stage of the growing season. Unlike the traditional fumigant and non-fumigant nematicides, MON 102133 SC Nematicide Seed Treatment makes management of nematodes more economical and practical because of its site-specific application, i.e. as a seed treatment. The registration of MON 102133 SC Nematicide Seed Treatment provides Canadian growers with the only conventional seed treatment product to manage nematode infestation on field corn and soybean. The product can also be applied in combination with certain fungicide and insecticide seed treatments.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of MON 102133 SC Nematicide Seed Treatment to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with tioxazafen on the skin or through inhalation of spray mists, anyone mixing, loading and applying MON 102133 SC Nematicide Seed Treatment must wear the following personal protective equipment: In

commercial seed treatment facilities and for commercial mobile treaters, workers mixing and loading must wear a long-sleeved shirt, long pants and chemical-resistant gloves; cleaners must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves; and baggers, sewers, stackers, and workers performing other activities not involving direct contact with treated seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves. Closed transfer mixing and loading is required for treating seed in commercial seed treatment facilities and for mobile treaters. Closed cab tractors are required when planting treated seed and planters must wear a work jacket over a long-sleeved shirt, long pants and chemical-resistant gloves for loading and sowing of treated seed.

Environment

Eating certain seed types treated with tioxazafen may pose a risk to birds and mammals. In order to reduce the risks, users will be required to bury or remove any spilled or exposed treated seed.

Next Steps

Before making a final registration decision on tioxazafen, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

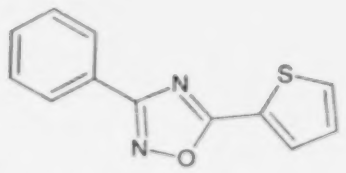
When the PMRA makes its registration decision, it will publish a Registration Decision on tioxazafen (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Tioxazafen

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Tioxazafen
Function	Nematicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	3-phenyl-5-(2-thienyl)-1,2,4-oxadiazole
2. Chemical Abstracts Service (CAS)	3-phenyl-5-(2-thienyl)-1,2,4-oxadiazole
CAS number	330459-31-9
Molecular formula	$C_{12}H_8N_2OS$
Molecular weight	228.27 g/mol
Structural formula	
Purity of the active ingredient	82.38 %

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—MON 102100 Technical

Property	Result
Colour and physical state	Cream to light gray solid
Odour	Faint aromatic odour
Melting point	109 °C
Boiling point or range	Not applicable
Bulk Density	0.513 – 0.674
Vapour pressure at 25°C	7.76E-05 Pa

Property	Result
Ultraviolet (UV)-visible spectrum	ε=1.728E+04 at λ=288.06nm ε=2.069E+04 at λ=246.05nm
Solubility in water at 20°C	1.24 µg/mL
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) Hexane — 6.64 Methanol — 11.1 n-Octanol — 13.3 Acetone — 100 Ethyl Acetate — 106 Toluene — 121 Dichloromethane — 284
n-Octanol-water partition coefficient (K_{ow})	4.13
Dissociation constant (pK_a)	Will be unionised in the environmental pH range
Stability (temperature, metal)	Stable for two weeks at 54 °C and on contact with metals and metal ions

End-Use Product—MON102133 Nematicide Seed Treatment

Property	Result
Colour	Brown
Odour	Slightly acrid
Physical state	Liquid
Formulation type	Suspension
Guarantee	537 g/L
Container material and description	High density polyethylene
Density	1170 g/L
pH of 1% dispersion in water	8.0 – 10.0
Oxidizing or reducing action	Not a strong oxidizing or reducing substance
Storage stability	Stable on storage at 55°C for 14 days
Corrosion characteristics	Not corrosive to commercial container material
Explodability	Not explosive

1.3 Directions for Use

To suppress certain soil-inhabiting nematodes, treat seeds with MON 102133 SC Nematicide Seed Treatment at 0.875 mL/1,000 seeds in field corn, or 0.438 mL/1,000 seeds in soybean. MON 102133 SC Nematicide Seed Treatment may be used in combination with the registered seed treatment products on crops for which they are labelled.

1.4 Mode of Action

Tioxazafen has a mode of action against soil-inhabiting nematodes. It causes a gene mutation that is selective to nematodes.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Soil and Water
High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) or gas chromatography with tandem mass spectrometry (GC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

Plant commodities
Method 115G806A, an electron spray ionization liquid chromatography method with tandem mass spectrometric detection (ESI LC-MS/MS), was developed and proposed for enforcement of tioxazafen and the metabolite benzamidine. This method fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation. Acceptable recoveries were obtained. The proposed enforcement method was successfully validated by an independent laboratory. Extraction solvents used in the method were similar to those used in the field corn, cotton and soybean metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method.

Method ME-1604, an electron impact ionization gas chromatography method with tandem mass spectrometric detection (EI GC-MS/MS), was developed and proposed for data generation of tioxazafen. Method ME-1579 (ESI LC-MS/MS) was developed and proposed for data generation of the metabolite benzamidine. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries were obtained. Adequate extraction efficiencies were demonstrated for both Method ME-1604 and Method ME-1579 using radiolabelled samples from the field corn (thinnings and stover) and soybean (hay and seed) metabolism studies.

Animal commodities

Method ME-1764 (EI GC-MS/MS and LC-MS/MS) was developed and proposed for data gathering and enforcement purposes of tioxazafen and the metabolites benzonitrile, benzamidine and 2-thenoylglycine. This method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries were obtained. The proposed enforcement method was successfully validated by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled goat (muscle, fat, kidney and milk) and hen (egg, fat) matrices analyzed with the proposed enforcement method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for tioxazafen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, mechanistic studies to support the proposed mode of action (MOA) for mouse liver tumour formation were submitted. Finally, several studies conducted with a photolyte of tioxazafen, identified as MON102130, were provided in the toxicology database. The above studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to tioxazafen.

The absorption, distribution, metabolism and excretion of tioxazafen, uniformly labelled with ^{14}C in the phenyl or thiophene ring, were investigated in rats. Rats received ^{14}C as a single oral low dose, single oral high dose, single low intravenous dose, or as the final dose following repeated low oral dosing of non-radiolabelled test material. Absorption of tioxazafen was rapid and high (approximately 80%) following administration of a single high oral dose, but slightly lower (approximately 65%) for the low dose. Following single or repeated oral dose administration, less than 1% of the administered dose (AD) remained in tissues after 7 days. The organs with the highest and longest lasting radioactivity levels were the liver, kidneys and renal cortex, with no apparent differences in tissue distribution with regards to sex, concentration, or position of the radiolabel. The adrenal glands also showed high radioactivity levels, with an approximate 2-fold increase in radioactivity levels in females, when compared to males. The half-life of elimination of tioxazafen from plasma was approximately 40 hours for the low and high dose regimens. Tioxazafen was excreted primarily in the feces (45-69% of the AD), followed by the urine (24-38% of the AD), with biliary excretion accounting for the majority of radioactivity in feces. Elimination via respired air was negligible. Tioxazafen was extensively metabolized with most metabolites representing less than 1% of the AD. In urine, the primary metabolite following administration of the phenyl radiolabel was benzamidine (up to 13% of the AD), followed by hydroxy tioxazafen glucuronide (up to 5% of the AD), and hippuric acid (up to 3% of the AD). For the thiophene-radiolabel, thenoylglycine (up to 6% of the AD), hydroxy tioxazafen glucuronide (up to 5% of the AD), and uncharacterized metabolite M26 (up to 4% of the AD) were the most abundant metabolites in urine. In feces, the only significant differences between position of radiolabels was that benzamidine was the most abundant metabolite (approximately

25% of the AD) in rats dosed with the phenyl radiolabel. The urinary metabolite, hydroxy tioxazafen glucuronide, was also identified in bile, where it was the most abundant metabolite, regardless of radiolabel. Unchanged tioxazafen was not detected in the excreta. The proposed metabolic pathways in rats involved oxidation (hydroxylation) of the thiophene ring, followed by conjugation primarily with glucuronic acid, and reductive cleavage and subsequent hydrolysis of the oxadiazole ring.

In acute toxicity testing, tioxazafen was of low toxicity via the oral, dermal and inhalation routes in rats. Tioxazafen was minimally irritating to the eyes and non-irritating to the skin of rabbits. In a dermal sensitization test using the Buehler method, tioxazafen was not a dermal sensitizer in guinea pigs.

The end-use product, MON102133 SC Nematicide Seed Treatment, was of low acute toxicity via the oral, dermal and inhalation routes in rats. In rabbits, it was non-irritating to the eyes and slightly irritating to the skin, and it was not a dermal sensitizer in guinea pigs using the Buehler method.

Following repeated dietary dosing in rats from short- to long-term duration, the adrenal gland was a target organ of toxicity. The adrenal effects included changes in organ weight, adrenocortical vacuolation and atrophy. Reduced body weights were also seen in most dietary studies as well as foreign material and/or brown pigment in the kidneys. The kidney findings were not accompanied by a suite of other renal effects, and were thus not considered adverse. Changes in hematology parameters, as well as in some clinical chemistry parameters, were also observed in several studies.

Hyperostosis of the femur, characterized as increased amounts of metaphyseal trabeculae filling the marrow space, was a common finding in the dietary studies in rats, occurring in several studies at doses that otherwise would define the NOAEL for the study. In determining the toxicological significance of these bone changes, other indications of impaired function resulting from occlusion of the marrow in the bone cavity caused by the excess bone growth were examined. Hyperostosis of the femur may have an adverse effect on haematopoiesis, and may also be associated with altered metabolism of calcium and phosphorus. Furthermore, a reduction in marrow cavity can have an impact on fat metabolism, which is linked to differentiation of bone marrow stromal cells. The only studies in which possible associative changes were observed were the short-term (28- and 90-day) dietary rat studies. In the 28-day dietary rat study, hyperostosis of the femur (graded as minimal) was observed in both sexes at a dose that resulted in an increase in adipose tissue in the bone marrow of the sternum in males. At the next highest dose, the adipose tissue of females was affected, and there were also other haematology changes possibly related to the hyperostosis. In the 90-day dietary rat study, minimal metaphyseal hyperostosis of the femur was observed at a lower dose in both sexes, with hematology changes occurring at the next higher dose, but in females only. In the reproductive toxicity, 90-day neurotoxicity, and 2-year chronic toxicity/oncogenicity studies in rats, minimal metaphyseal hyperostosis of the femur was observed in both sexes only at the high dose and in the absence of possible associative changes. Overall, the low incidences and minimal level of severity of the hyperostosis at the lower doses in the rat studies, combined with the lack of any clear indication of correlative toxicity, indicated a low level of concern for the bone changes. Further, there was

no indication that the level of severity increased with increasing duration of dosing. It is also important to note that there was no indication of adverse changes in ossification parameters in the developing fetus in the developmental toxicity studies.

Following repeated dietary dosing in mice of short- to long-term duration, the liver was the primary target organ of toxicity. Centrilobular hepatocellular hypertrophy was observed in both sexes for all durations of exposure. Increases in liver weights, bilirubin, and cholesterol, as well as changes in liver enzymes were also indicative of liver toxicity. Female mice appeared to be more sensitive to the liver effects than males, as single cell necrosis and scattered necrotic hepatocytes were apparent in females, but not in males. In addition, female mice exhibited decreased survival following long-term dosing. In the short-term studies, there were incidences of female deaths occurring earlier than, or in the absence of, male deaths at the same dose level.

Following 90-day dosing in dogs via capsule with tioxazafen, increased lung weights were observed in both sexes at the highest dose level. There was no indication of functional impairment and no adverse lung pathology; therefore, there was a low level of concern for this finding. One female dog was found dead on study day 3. Although there was ulceration of the larynx, suggesting a physical or irritant cause such as might be triggered by regurgitation/aspiration, and yellow emesis was observed in the animal's enclosure, the cause of death was undetermined. Upon consideration of the low incidences of emesis in the study, this death was considered equivocal in terms of its relationship to treatment.

There was evidence in the database suggesting increased toxicity with increasing duration of dosing with tioxazafen. Mortality and liver necrosis (scattered necrotic hepatocytes) were observed in mice after longer-term dosing at lower dose levels than those resulting in the same effects in the short-term studies.

Following short-term (28-day) repeated dermal exposure to tioxazafen, epidermal hyperplasia was noted in rats at all dose levels; however, there was no dermal irritation at the site of dosing. Vacuolation of the adrenal cortex was observed in male rats at all dose levels, whereas this finding was observed only in high-dose females. Other noteworthy findings at higher dose levels included changes in the weights of various organs, including increases in lung weight without corresponding histopathology, as well as clinical chemistry changes and effects on body weight.

Effects associated with treatment with tioxazafen in the 28- and 90-day nose-only exposure inhalation toxicity studies were observed at similar dose levels and included atrophy and vacuolation of the adrenal glands as well as hyperplasia of the respiratory epithelium. An increase in incidence and severity of respiratory epithelial hyperplasia was observed. Higher dose levels also resulted in degeneration of the respiratory epithelium, lymphocyte infiltrate in the nasal cavity, lymphoid hyperplasia of the nasal cavity, and squamous metaplasia of the respiratory epithelium. The level of concern for the hyperplastic findings in respiratory epithelium at the lower dose level was low, as it was noted that the level of severity was minimal to mild, there was no indication of functional impairment (that is, degeneration), and since there was no laryngeal involvement as only the upper nasal sections (primarily sections II and III) were affected.

Reproductive toxicity was investigated in a dietary 2-generation study in the rat. Increased adrenal weights and vacuolation were noted at lower doses in males. Food consumption and body weight were affected at higher doses, as was the liver. There were no effects on the offspring or any reproductive parameter at any dose level. There was no evidence of sensitivity of the young.

In gavage developmental toxicity studies in rats and rabbits, there was no evidence of sensitivity of the young. In rats, the dams exhibited decreased body weight (including body weight loss) and decreased adrenal weights at doses that produced no effects on the fetus. In rabbits, although there were no effects noted in dams or fetuses at the highest dose level, body weight loss and decreased body weight gain were noted in dams in the range-finding study at the same dose level.

There was no evidence of genotoxicity when tioxazafen was tested in a battery of in vivo and in vitro genotoxicity studies. The end-use product, MON102133 SC Nematicide Seed Treatment, was negative in a bacterial reverse mutation assay but produced a positive result in the in vivo mouse micronucleus assay, at the 24-hour harvest for the high dose only.

Results from the 18-month mouse oncogenicity study with tioxazafen indicated a treatment-related increased incidence of hepatocellular carcinomas and systemic hemangiosarcomas in male mice at the highest dose level. A proposed MOA for the formation of liver hepatocellular tumours was provided. The key events in this MOA included (1) cytotoxicity with associated cytochrome P450 induction and hepatocellular hypertrophy, (2) hepatocellular proliferation, (3) selective clonal expansion leading to altered foci, and (4) hepatocellular adenomas and carcinomas. Additional investigations were performed to elucidate the proposed MOA. These consisted of immuno-histochemical staining of livers from the short-term mouse studies to examine liver cell proliferation (Ki67 antibody) and peroxisome proliferation (PMP70 and catalase antibodies), and 4- and 14-day dietary studies in the mouse examining clinical pathology and histology, with immune-histochemical, enzyme and gene expression profiling relating to a CAR/PXR MOA. In consideration of the findings in these studies, as well as the overall information in the database, the proposed MOA was deemed plausible to address the mouse hepatocellular carcinomas. No MOA was proposed for the induction of the systemic hemangiosarcomas in male mice; therefore, a linear low-dose extrapolation approach (q_1*) for the cancer risk assessment was deemed appropriate to address this tumour type. An increased incidence of histiocytic sarcomas was noted in female mice at the highest dose level. In consideration of the dose levels where deaths occurred in female mice and the liver effects observed (liver necrosis), it was concluded that the highest dose in the 18-month oncogenicity study was excessive in female mice. For this reason, the increased tumour incidences in females at this dose level were considered not relevant for risk assessment.

In the tioxazafen rat carcinogenicity study, all male dose groups were terminated four weeks earlier than the scheduled sacrifice due to non- treatment-related low survival in the low-mid dose group; this did not impact the utility of this study. The incidence of thoracic cavity hibernomas was increased in males at the two highest dose levels and in females at the highest dose level. Hibernomas are rare neoplasms that originate in brown adipose tissue. Given the nature of the tumour, the findings represent those tumours detected at gross examination only

and thus not all animals were routinely examined to detect this tumour type. For these reasons, the increased incidences of hibernomas at the two highest dose levels in male rats, although not clearly dose-responsive, were considered equivocal. In females, the numerical increase in hibernomas was of concern at the highest dose level only. Although not clearly dose-responsive, there was also an increased incidence of benign endometrial stromal tumours (polyps) in females at the two highest doses. There was no increase in malignant endometrial tumours. Overall, the increased incidence of endometrial polyps at the two highest dose levels was considered equivocal.

The potential for tioxazafen to produce neurotoxic effects was investigated in rats following acute gavage and 90-day dietary dosing. Following administration of a single dose, reductions in total motor and ambulatory activity counts were noted on the day of dosing in conjunction with decreased body temperature. Additionally, decreased defecation and body weight gain were noted during the first week following dosing. The time to peak effect was reported as 4 hours. Decreased body weight, body weight gain and food efficiency were observed in the 90-day study and at the highest dose level, minimal metaphyseal hyperostosis in the femur as previously discussed. There were no neuropathological findings observed in either study. Overall, there was no evidence that tioxazafen was selectively neurotoxic.

In a 28-day immunotoxicity study in mice in which tioxazafen was administered in the diet, there was indication of perturbation/dysregulation of the immunologic response in the form of decreased serum IgM response in addition to effects on the liver.

A rat acute oral toxicity study and a 28-day dietary toxicity study in rats, as well as genotoxicity studies, were available for photolyte MON102130, a major environmental metabolite. The acute study revealed low oral toxicity. A comparison of the clinical findings in the rat acute oral limit dose studies for the photolyte and tioxazafen suggested that the photolyte was more acutely toxic than tioxazafen; however, differences in vehicles may have factored into this finding. Results from the 28-day study showed a similar spectrum of toxicity (effects at comparable doses levels) to that of tioxazafen. A bacterial reverse mutation assay and an in vivo mouse micronucleus assay were negative.

Results of the toxicology studies conducted on laboratory animals with TIOXAZAFEN, its associated end-use product MON102133 SC Nematicide Seed Treatment, and the photolyte MON102130 are summarized in Appendix I, Tables 2, 3 and 4, respectively. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Incidents were searched for the active ingredient tioxazafen. No human or domestic animal incidents involving the active ingredient tioxazafen have been reported to the PMRA and the applicant did not submit any additional data.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies including developmental toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats was available.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. There were no fetal effects observed in the rat and rabbit developmental toxicity studies, and no effects on offspring were noted in the 2-generation rat reproductive toxicity study. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold for all scenarios.

3.2 Acute Reference Dose (ARfD)

To estimate acute dietary risk, the acute oral neurotoxicity study conducted in adult rats with a LOAEL of 250 mg/kg bw was selected. At the LOAEL of 250 mg/kg bw, which represented the lowest dose level tested, decreased total motor and ambulatory activity counts were observed in both sexes at the time of peak effect. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. A 3-fold database uncertainty factor was applied for the use of a LOAEL. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 300.
The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{250 \text{ mg/kg bw}}{300} = 0.8 \text{ mg/kg bw of tioxazafen}$$

3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the two-generation reproductive toxicity study in the rat with a NOAEL of 5 mg/kg bw/day was selected. At the LOAEL of 20 mg/kg bw/day, increased adrenal weight and adrenocortical vacuolation were observed in males. The selected NOAEL was considered to provide adequate protection for all populations. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section. The composite assessment factor (CAF) is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5 \text{ mg/kg bw/day}}{100} = 0.05 \text{ mg/kg bw/day of tioxazafen}$$

The ADI provides a margin of approximately 300 to the dose level at which an equivocal increase in hibernomas was observed in male rats, and a margin of approximately 1000 to the dose level at which hibernomas were observed in female rats. It provides a margin of 320 to the dose level at which an equivocal increase in benign endometrial stromal polyps was observed in female rats. It also provides a margin of approximately 5600 to the dose at which hepatocellular carcinomas were observed in male mice.

Cancer Assessment

There was sufficient evidence to support the proposed MOA for the liver hepatocellular carcinomas in male mice. The ADI and selected MOEs for occupational exposure provide sufficient margins to these liver hepatocellular carcinomas as well as to the hibernomas and equivocal benign endometrial stromal tumours noted above.

Systemic hemangiosarcomas were observed in male mice administered tioxazafen in the diet for 18 months. No proposed MOA was provided for induction of these tumours. Therefore, a linear low-dose extrapolation approach for the cancer risk assessment was deemed appropriate. The cancer unit risk (q_1*) for systemic hemangiosarcomas in male mice is 3.41×10^{-3} (mg/kg bw/day)$^{-1}$.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal

For short- and intermediate-term dermal risk assessments, the 28-day dermal toxicity study in rats was selected. At the LOAEL of 100 mg/kg bw/day, epidermal hyperplasia and adrenocortical vacuolation were observed. No NOAEL was established in this study. For occupational scenarios, the target Margin of Exposure (MOE) is 300, which includes uncertainty factors of 10-fold each for interspecies extrapolation and intraspecies variability as well as a 3-fold factor for the use of a LOAEL. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- and Intermediate-term Inhalation

For short- and intermediate-term inhalation risk assessments, the NOAEC of 15 mg/m^3 (3.9 mg/kg bw/day) from the combined results from the 28-day and 90-day inhalation toxicity studies in rats was selected. At the LOAEC of 50 mg/m^3 (13 mg/kg bw/day), decreased body weights in conjunction with adrenocortical vacuolation and atrophy were observed. For occupational scenarios, the target MOE is 100, which includes uncertainty factors of 10-fold each for interspecies extrapolation and intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Combined MOE for Occupational Exposure Assessments

It was determined that adrenocortical vacuolation was a common endpoint via the dermal and inhalation routes. Therefore, it was considered appropriate to assess combined exposure values via the dermal and inhalation routes for mixer/loader/applicators handling MON102133 SC Nematicide Seed Treatment, and to compare them to the endpoints and corresponding MOEs established for short- to intermediate-term dermal and inhalation exposures.
Occupational exposure to tioxazafen is characterized as short- to intermediate-term in duration for seed treatment workers and short-term for planting treated seed, and occurs predominantly by the dermal and inhalation routes. Dermal and inhalation exposures can be combined as there are common toxicological endpoints of concern for both exposure routes.

Dermal Absorption

A rat in vivo study, a rat in vitro study and a human in vitro study were submitted to support the registration of tioxazafen. The rat in vivo study was found to be unacceptable for determining a dermal absorption value for tioxazafen due primarily to the consistent high recovery of the administered dose in the dressings at all dose levels and sacrifice groups (ranging from 66-97%). The rat and human in vitro studies were acceptable, however; in vitro animal and/or human data alone are considered insufficient for determining the dermal absorption pattern of a given pesticide. As the in vivo dermal absorption study was found to be unacceptable, the in vitro studies were used as part of the weight of evidence approach to reduce the default dermal absorption value of 100% to 50%. In addition to the dermal absorption studies, this included an assessment of the physical and chemical properties of the active ingredient and the end-use product.

3.1.2 Occupational Exposure and Risk

Field corn and soybean seed can be treated with MON 102133 SC Nematicide Seed Treatment in commercial seed treatment facilities and by commercial mobile treaters, and can be planted using conventional seeding equipment.

3.4.2.1 Dust-off Study

A dust-off study was submitted to support the occupational exposure assessment of MON 102133 SC Nematicide Seed Treatment to bridge surrogate wheat seed treatment and surrogate field corn planting exposure studies to field corn and soybean seed treated with MON 102133 SC Nematicide Seed Treatment.
The study adequately shows that the dust-off potential of field corn and soybean seed treated with MON 102133 SC Nematicide Seed Treatment are generally lower than that from surrogate exposure study test material treated crops. Therefore, the surrogate studies are not expected to underestimate exposures to MON 102133 SC Nematicide Seed Treatment treated seed based on the dust-off data provided.

3.4.2.2 Commercial Seed Treatment Exposure and Risk Assessment

Individuals have potential for exposure to tioxazafen while treating seed in commercial seed treatment facilities and by commercial mobile treaters. Chemical specific data for assessing human exposure during commercial seed treatment were not submitted. As such, surrogate exposure data were used to estimate risk to workers in commercial seed treatment settings.

Dermal and inhalation exposure estimates were derived for workers treating field corn and soybean seed with MON 102133 SC Nematicide Seed Treatment using closed transfer commercial treating equipment, as well as workers bagging, sewing and stacking bags of treated seed and cleaners. The exposure estimates are based on treaters wearing a long-sleeved shirt, long pants and chemical-resistant gloves; cleaners wearing chemical-resistant coveralls over a long-sleeved shirt, long pants, and chemical-resistant gloves; and baggers, sewers, stackers, and workers performing other activities not involving direct contact with treated seed wearing a long-sleeved shirt, long pants and chemical-resistant gloves.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day. No dermal absorption value was required for the non-cancer assessment, as the non-cancer dermal endpoint was selected from a dermal toxicity study. A 50% dermal absorption value was used for the cancer risk assessment. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL; no observed adverse effects levels) to obtain the margin of exposure (MOE) for the non-cancer health risk assessment; the target MOE is 300 for dermal exposure and 100 for inhalation exposure. The MOEs were then combined to calculate the Aggregate Risk Index (ARI) for combined dermal and inhalation exposures.

A cancer quotient (q_1*) was determined and, therefore, a cancer risk assessment was required for occupational exposure. Cancer risk is estimated by extrapolating the average daily dose (ADD) over an average lifetime worked to obtain a lifetime average daily dose (LADD). The LADD is compared to the cancer risk quotient to determine the cancer risk. Workers performing commercial treatment are expected to work 61 days per year for field corn and 22 days for soybean seed treatment and may work up to 40 years in a commercial facility. A cancer risk below 1×10^{-5} is generally considered acceptable in worker populations.

Table 3.4.2.2.1 presents the non-cancer health risk estimates for the commercial seed treatment of field corn and soybean seed with MON 102133 SC Nematicide Seed Treatment. The calculated Aggregate Risk Index (ARI) was above the target for the combined dermal and inhalation exposures. No non-cancer health risks of concern were identified for exposure to tioxazafen for treating field corn and soybean seed using closed transfer equipment in commercial facilities when workers wear the personal protective equipment as worn in the surrogate study.

Table 3.4.2.2.1 Tioxazafen Commercial Treating Exposure and Non-Cancer Risk Assessment for MON 102133 SC Nematicide Seed Treatment

Task	Seed treated per day (kg) [1]	Application rate (g a.i./100 kg seed)	Unit exposure (µg a.i./kg a.i.) [2]		Exposure [3 4] (mg/kg bw/day)		Margin of Exposure (MOE) [6]		
			Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	ARI [7]
Field Corn									
Treater	125,000	175	0.88	0.016	2.41E-	4.38E-05	41,600	89,100	120

					03				
Bagger	125,000	175	17.67	0.89	4.83E-02	2.43E-03	2,070	1,600	4.8
Cleaner	--	175	18.46	0.64	4.04E-02	1.40E-03	2,480	2,790	6.4
Cleaner + Treater[5]	--	--	--	--	4.28E-02	1.44E-03	2,340	2,700	6.0
Soybean									
Treater	63,000	155	0.88	0.016	1.07E-03	1.95E-05	93,100	200,000	270
Bagger	63,000	155	17.67	0.89	2.16E-02	1.09E-03	4,640	3,590	11
Cleaner[4]	--	155	18.46	0.64	3.58E-02	1.24E-03	2,800	3,150	7.2
Cleaner + Treater[5]	--	--	--	--	3.68E-02	1.26E-03	2,710	3,100	7.0

[1] From the Commercial Throughputs Final Memo (AHETF, 2013).
[2] Arithmetic mean values (µg a.i./kg a.i.) from the surrogate exposure study. Cleaner unit exposure values are in µg/g a.i./100 kg seed.
[3] Exposure = (Seed treated per day × App rate × Unit exposure)/(80 kg bw × 1000 µg/mg)
[4] Cleaner Exposure = (Unit exposure × rate in g a.i./100 kg seed)/(80 kg bw × 1000 µg/mg)
[5] Cleaner and treater exposures were combined as treaters would also do cleaning tasks.
[6] Dermal: based on LOAEL = 100 mg /kg bw/day, target MOE = 300; Inhalation = 3.9 mg/kg bw/day, target MOE = 100
[7] ARI = Aggregate Risk Index = 1/(Dermal target MOE/Dermal MOE + Inhalation target MOE/Inhalation MOE). An ARI above 1 is considered acceptable.

Table 3.4.2.2.2 presents the cancer risk estimates for the commercial seed treatment of field corn and soybean seeds with MON 102133 SC Nematicide Seed Treatment. No cancer risks of concern were identified for exposure to tioxazafen for workers using closed transfer equipment in commercial facilities when wearing the personal protective equipment as worn in the surrogate study.

Table 3.4.2.2.2 Tioxazafen Commercial Treating Exposure and Cancer Risk Assessment for MON 102133 SC Nematicide Seed Treatment

Task	Seed treated per day (kg) [1]	Application rate (g a.i./100 kg seed)	Unit exposure (µg a.i./kg a.i.) [2]		Exposure [3] (mg/kg bw/day)		LADD [6] (mg/kg bw/day)	Cancer Risk [7]
			Dermal	Inhalation	Dermal	Inhalation		
Field Corn								
Mixer/loader	90,000	175	0.88	0.016	8.66E-04	3.15E-05	7.69E-05	3E-07
Bagger	90,000	175	17.67	0.89	1.74E-02	1.75E-03	1.64E-03	6E-06
Cleaner	--	175	18.46	0.64	2.02E-02	1.40E-03	1.85E-03	6E-06
Cleaner + Treater[5]	--	--	--	--	2.11E-02	1.43E-03	1.93E-03	7E-06
Soybean								
Mixer/loader	31,000	155	0.88	0.016	2.64E-04	9.61E-06	8.47E-06	3E-08

Task	Seed treated per day (kg) [1]	Application rate (g a.i./100 kg seed)	Unit exposure (µg a.i./kg a.i.) [2]		Exposure [3] (mg/kg bw/day)		LADD [6] (mg/kg bw/day)	Cancer Risk [7]
			Dermal	Inhalation	Dermal	Inhalation		
Bagger	31,000	155	17.67	0.89	5.31E-03	5.35E-04	1.81E-04	6E-07
Cleaner[4]	--	155	18.46	0.64	1.79E-02	1.24E-03	5.91E-04	2E-06
Cleaner + Treater[5]	--	--	--	--	1.81E-02	1.25E-03	6.00E-04	2E-06

[1] From the Commercial Throughputs Final Memo (AHETF, 2013).
[2] Arithmetic mean values (µg a.i./kg a.i.) from the surrogate exposure study. Cleaner unit exposure values are in µg/g a.i./100kg seed.
[3] Exposure = (Seed treated per day × App rate × Unit exposure × Dermal absorption)/(80 kg bw × 1000 µg/mg)
[4] Cleaner Exposure = (Unit exposure × rate in g a.i./100 kg seed × Dermal absorption)/(80 kg bw × 1000 µg/mg)
[5] Cleaner and treater exposures were combined as treaters would also do cleaning tasks.
[6] Lifetime adjusted daily dose (LADD) (mg/kg bw/day) = (Exposure × days of exposure per year × 40 years of exposure) / 365 days × 78 years
[7] Cancer risk = LADD × q_1*; q_1* = 3.41×10^{-3} $(mg/kg\ bw/day)^{-1}$

3.4.2.3 Planting Exposure and Risk Assessment

Workers have potential for exposure to tioxazafen while planting treated seed. Chemical specific data for assessing human exposure during planting of treated seed were not submitted. As such, surrogate planting exposure data were used to estimate risk to workers planting treated seed.

Dermal and inhalation exposure estimates were derived for workers planting field corn and soybean seed with MON 102133 SC Nematicide Seed Treatment using closed-cab tractors. The exposure estimates are based on planters wearing a work jacket over a single layer and chemical-resistant gloves for loading and sowing of treated seed.

Dermal exposure was estimated by coupling the unit exposure values with the amount of treated seed planted per day. No dermal absorption value was required for the non-cancer assessment, as the non-cancer dermal endpoint was selected from a dermal toxicity study. A 50% dermal absorption value was used for the cancer risk assessment.

Inhalation exposure was estimated by coupling the unit exposure values with the amount of treated seed planted per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAEL) to obtain the MOE for the non-cancer health risk assessment; the target MOE is 300 for dermal exposure and 100 for inhalation exposure. The MOEs were then combined to calculate the Aggregate Risk Index (ARI) for combined dermal and inhalation exposures.

A cancer quotient (q_1*) was determined and, therefore, a cancer risk assessment was required for occupational exposure. Cancer risk is estimated by extrapolating the average daily dose (ADD) over an average lifetime worked to obtain a lifetime average daily dose (LADD). The LADD is compared to the cancer risk quotient to determine the cancer risk. Workers planting treated seed

are expected to work 30 days per year and may work up to 40 years. A cancer risk below 1×10^{-5} is generally considered acceptable in worker populations.

Table 3.4.2.3.1 presents the non-cancer health risk estimates for planting field corn and soybean seeds treated with MON 102133 SC Nematicide Seed Treatment. The calculated Aggregate Risk Index (ARI) was above the target for the combined dermal and inhalation exposures. No non-cancer health risks of concern were identified for exposure to tioxazafen for planting field corn and soybean seed with closed-cab tractors and wearing the personal protective equipment as worn in the surrogate study.

Table 3.4.2.3.1 Tioxazafen Planting Exposure and Risk Assessment for MON 102133 SC Nematicide Seed Treatment

Task	Seed treated per day (kg)[1]	Application rate (g a.i./100 kg seed)	Unit exposure [2] (ug a.i./kg a.i.)		Exposure [3] (mg/kg bw/day)		MOE [4]		
			Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	ARI [5]
Field Corn	1,350	175	1154	82.83	0.0341	0.00245	2,930	1,590	6.1
Soybean	9,000	155	1154	82.83	0.201	0.0144	497	270	1.0

[1] From the Seed Treated Planted Per Day Table (2009).
[2] Arithmetic mean values used from the surrogate exposure study.
[3] Exposure = (Seed treated per day × App rate × Unit exposure)/(80 kg bw × 1000 µg/mg)
[4] Dermal LOAEL = 100 mg/kg bw/day, target MOE = 300; Inhalation NOAEL = 3.9 mg/kg bw/day, target MOE = 100
[5] ARI = Aggregate Risk Index = 1/(Dermal target MOE/Dermal MOE + Inhalation target MOE/Inhalation MOE). An ARI above 1 is considered acceptable.

Table 3.4.2.2.2 presents the cancer risk estimates for planting field corn and soybean seed treated with MON 102133 SC Nematicide Seed Treatment. No cancer risks of concern were identified for exposure to tioxazafen for workers planting treated seed when wearing the personal protective equipment as worn in the surrogate study.

Table 3.4.2.3.2 Tioxazafen Planting Cancer Risk Assessment for MON 102133 SC Nematicide Seed Treatment

Task	Seed treated per day (kg) [1]	Application rate (g a.i./100 kg seed)	Unit exposure [2] (ug a.i./kg a.i.)		Exposure [3] (mg/kg bw/day)		LADD [4] (mg/kg bw/day)	Cancer Risk [5]
			Dermal	Inhalation	Dermal	Inhalation		
Field Corn	1,350	175	1154	82.83	0.0170	0.00245	8.21E-04	3E-06
Soybean	5,400	155	1154	82.83	0.0604	0.00867	2.91E-03	1E-05

[1] From the Seed Treated Planted Per Day Table (2009).
[2] Arithmetic mean values used from the surrogate exposure study.
[3] Exposure = (Seed treated per day × App rate × Unit exposure × Dermal absorption)/(80 kg bw × 1000 µg/mg)
[4] LADD (mg/kg bw/day) = (ADD × 30 days of exposure per year × 40 years of exposure) / 365 days × 78 years
[5] Cancer risk = LADD × q_1*; q_1* = 3.41×10^{-3} (mg/kg bw/day)$^{-1}$

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Bystander Exposure and Risk

Bystander exposure is expected to be negligible since bystanders are not expected to be in the vicinity where seeds are treated. Furthermore, the product is liquid and applied using closed transfer treatment equipment in commercial seed treatment facilities or by commercial mobile treaters. Bystander exposure should be negligible since the potential for drift is expected to be minimal when planting treated seed.

3.5 Dietary Exposure Assessment

3.5.1 Residues in Drinking Water

The residue definition for environmental and drinking water assessments includes the parent, tioxazafen (TIOXAZAFEN), and the major transformation products: 3-thienyl102100, TIOXAZAFEN iminoamide and benzamidine. The major transformation product thiophene acid is not included in the residue definition as it is expected to be excreted more rapidly in the rat than the parent, is non-persistent and is expected to mineralize in the environment.

The parent and transformation products were modelled considering their transformation relationship in soil and water. Their estimated environmental concentrations (EECs) were then added up to calculate the combined residue EECs. The fate of tioxazafen was modelled for both drinking water exposure to humans and for exposure to aquatic organisms considering an application rate of 250 g a.i./ha. The proposed maximum rate for this submission 125g a.i./ha and therefore the results of the modelling is conservative and protective for all labelled uses in Canada. Application information and the main environmental fate characteristics used in the model are summarized in Appendix I, Table 16.

Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

Estimated environmental concentrations (EECs) of the combined residue (tioxazafen and its three transformation products 3-thienyl 102100, MON 102100 iminoamide (IMI) and benzamidine (BEN)) in potential drinking water sources (groundwater and surface water) were estimated using the PWC (Pesticide in Water Calculator) model to simulate both leaching through a layered soil profile over a 50-year period, where concentrations were calculated from the average concentrations in the top 1m of the water table or pesticide runoff from a treated field into an adjacent water where EECs are the average concentration in the water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario for seed treatment only. These EEC estimates may allow for future use expansion into other crops at this application rate for seed treatment only.

Appendix I, Table 16 lists the application information and main environmental fate characteristics used in the simulations. Nine initial application dates between April and June were modelled. The models were run for 50 years for all scenarios. The largest EECs of all selected runs are reported in the table below.

Table 3.5.1.1 Level 1 estimated environmental concentrations of the combined residue of tioxazafen and its three transformation products 3-thienyl 102100, MON 102100 iminoamide and benzamidine in potential drinking water

Use pattern	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
1 × 250 g a.i./ha	0.021	0.021	1.1	0.12

Notes:
1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of daily peak concentrations
4 90th percentile of yearly average concentrations

3.5.2 Residues in Plant and Animal Foodstuffs

Plant commodities

The residue definition for risk assessment and enforcement in commodities of plant origin is tioxazafen and the metabolite benzamidine. The data gathering and enforcement analytical methods are valid for the quantitation of tioxazafen and benzamidine residues in crop matrices.

The residues of tioxazafen and benzamidine are stable in representative matrices from five crop categories (high water, high oil, high protein, high starch and high acid content) for at least 9 months when stored at ~-20°C. Therefore, tioxazafen and benzamidine residues are considered stable in all frozen crop matrices and processed crop fractions for up to 9 months.

The raw agricultural commodities (RACs) soybean seed and field corn grain were processed, but not undelinted cotton seeds as there were no quantifiable residues of tioxazafen or benzamidine in the RAC. Processing factors could not be determined for field corn given that there were no quantifiable residues of either tioxazafen or the metabolite benzamidine in the grain RAC or in the processed fractions (grits, meal, flour, starch, and oil). For soybean, residues of benzamidine concentrated only in meal (median processing factor = 1.4x) and toasted meal (median processing factor = 1.6x), and processing factors could not be determined for tioxazafen as there were no quantifiable residues in the soybean seed RAC or in the processed fractions (meal, toasted meal and oil).

Crop field trials conducted throughout the United States including Canadian representative growing regions using end-use products containing tioxazafen at approved or exaggerated rates in or on field corn, imported cotton and soybean are sufficient to support the proposed maximum residue limits.

Animal commodities

The residue definition for risk assessment and enforcement in commodities of animal origin is tioxazafen and the metabolite benzamidine.

The data gathering/enforcement analytical method is valid for the quantitation of tioxazafen and benzamidine residues in livestock matrices.

Residues of tioxazafen and the metabolite benzamidine are stable at -18°C for at least 7 months in milk, liver, kidney and muscle, and for at least 6 months in fat and eggs; residues of the metabolite thenoylglycine are stable at -18°C in milk, liver and kidney for at least 7 months; and residues of metabolite benzonitrile are stable at -18°C in fat for at least 6 months.

Adequate feeding studies were conducted with dairy cattle and laying hens to assess the anticipated residues in livestock matrices resulting from the current uses.

3.5.3 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™) program which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/ WWEIA) dietary survey.

3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for tioxazafen: 100% crop treated, default processing factors and residues in/on crops and animal commodities at MRL levels. The basic chronic dietary exposure from all supported tioxazafen food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than or equal to 2.1% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to tioxazafen from food and drinking water is 0.4% of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 2.2% (0.001078 mg/kg bw/day) of the ADI.

The cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment. The lifetime cancer risk from exposure to tioxazafen in food and drinking water was estimated to be 7×10^{-7} for the general population, which is not of health concern.

3.5.3.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for tioxazafen: 100% crop treated, default processing factors and residues in/on crops and animal commodities at MRL levels. The basic acute dietary exposure (food alone) for all supported tioxazafen registered commodities is estimated to be <1% of the ARfD for all population subgroups (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: <1% of the ARfD for all population subgroups.

3.5.4 Aggregate Exposure and Risk

The aggregate risk for tioxazafen consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.5 Maximum Residue Limits

Table 3.5.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Dry soybeans	0.04
Field corn; undelinted cotton seeds; eggs; fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; and milk	0.02

For additional information on Maximum Residue Limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The analytical methodologies, nature of the residues in animal and plant matrices, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 6 and 7.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physico-chemical properties, tioxazafen does not dissociate under environmentally relevant conditions, is sparingly soluble in water, is not likely to volatilize from water or moist soil under field conditions and has low potential for long-range atmospheric transport.

Abiotic processes including hydrolysis, volatilization and phototransformation are not expected to contribute to the overall dissipation of tioxazafen in soil. Laboratory studies indicate that tioxazafen is slightly persistent to persistent in aerobic and anaerobic (flooded) soils, depending on soil type. It dissipates through biotransformation and through the formation of unextracted residues. Additional extraction techniques using a variety of solvents with a range of dielectric constants did not succeed at extracting the residues. The unextracted residues were therefore considered not readily bioavailable and not included in half-life estimates. A minimal amount of mineralization was observed in laboratory studies (up to 20% of the applied radioactivity –AR- as CO_2), major transformation products (> 10% of the applied radioactivity) were only observed under anaerobic conditions. Minor transformation products did not accumulate to significant levels over the duration of the studies and are not expected to be of concern when tioxazafen is used as a seed treatment.

A terrestrial field study was conducted as in-furrow applications as well as with treated seeds in four North-American sites. Only the plots in Manitoba were in a Canadian-relevant ecoregion. Tioxazafen was more persistent at the Manitoba site, with DT_{50}s of 220 d and 73.1 d for treated seeds and in-furrow plots, respectively. Corresponding representative half-lives were 552 and 219 days, and DT_{90}s of 1500 and 729 days. Representative half-lives were significantly higher than DT_{50}s, indicating that tioxazafen does not dissipate following an exponential decay (SFO), but that its dissipation slows down at some point. Results from the Manitoba site indicated that tioxazafen has the potential to carry over in soil, with more than 30% of the applied tioxazafen being found at the beginning of the following growing season. Tioxazafen dissipated with significantly lower DT50s in the American sites (Illinois, Nebraska and Georgia), which are not in Canadian-relevant ecoregions; DT_{50}s were 44.7, 26.9 and 94.3 d for treated seed plots, and 36.7,101 and 40.1 d for in-furrow plots, in Illinois, Nebraska and Georgia, respectively. Corresponding representative half-lives were 94.6 and 94.3 d for treated seed plots, and 220, 101 and 100 d for in-furrow plots; corresponding DT_{90}s were 149, 44.7, 314 and 313 days for treated seed plots, and 530, 336 and 332 days for in-furrow plots.

Tioxazafen is considered slightly mobile to immobile in soil as it sorbs strongly to soil. The method of Gustafson (1989) may be used to estimate the leaching potential of pesticides. The GUS score calculated from half-lives and adsorption coefficients in different soils classifies tioxazafen as a non-leacher. It is unlikely to leach through soil and reach groundwater. This is supported by its intrinsic physico-chemical properties, the results of laboratory studies, as well as water modelling results indicating that groundwater concentrations are expected to be low. Terrestrial field dissipation studies showed that tioxazafen remained in the top 30 cm and was not detected deeper in the soil profile.

Section 1.2 "Physical and Chemical Properties of the Active Ingredient and End-Use Product" presents the physical and chemical properties that influence the fate of tioxazafen in the environment. In Appendix I, Table 8 presents transformation products of tioxazafen, and Appendix I, Table 9 presents a summary of all environmental fate studies of transformation and mobility.

Although the use pattern of MON102133 Nematicide Seed Treatment does not include direct application to water, it may enter the aquatic environment through runoff from the field where treated seeds were planted. Tioxazafen has low water solubility and, in the aquatic environment, it partitions in both the water and the sediment layers. Tioxazafen is stable to hydrolysis. Tioxazafen can photolyse to the structurally similar isomer, MON102130 (3-thienyl 102100); however, this is not considered a degradation reaction. It is non-persistent in aerobic and anaerobic water-sediment systems due to microbial transformation and the formation of unextracted residues that are not readily bioavailable.

Significant mineralization of tioxazafen occurred due to biotransformation in aerobic systems, with the formation of the major transformation products tioxazafen-iminoamide, benzamidine and thiophene acid, as well as some minor transformation products that did not accumulate to significant levels over the duration of the studies; although there were deficiencies associated with the biotransformation studies in aquatic systems, they were found acceptable to estimate the dissipation time of tioxazafen and support the use as seed treatment due to the expected low environmental exposure; In the event of a request for use expansion, an additional evaluation of the data may be required to determine whether new studies are required.

The log Kow and BCF value indicate that tioxazafen has the potential to accumulate in the tissues of aquatic organisms, but are below the bioaccumulation criterion of 5000. According to an atmospheric transport model (AOPWIN v1.92), tioxazafen has an atmospheric half-life of 5.4 hours which is below the 2 day half-life indicating the potential for long range transport. Tioxazafen does not meet the TSMP criterion for bioaccumulation and is not expected to undergo long range transport.

Laboratory studies conducted with MON102130 indicate that it is toxic to aquatic organisms. There were no ecotoxicity or environmental fate data submitted to characterise the other transformation products; therefore, they were assumed to be of equal toxicity to the parent, and estimated environmental concentrations were calculated from the combined residues of the active ingredient and the major transformation products. Ecotoxicity information is found in Appendix I, Table 10 and Table 11. Even though thiophene acid is a major transformation product in water-sediment systems, it is not considered to be of environmental significance due to its rapid mineralization. Therefore the residues considered relevant to the environment include the parent, tioxazafen, as well as the major transformation products MON102130, 3-thienyl-102100, tioxazafen -iminoamide and benzamidine, but exclude thiophene acid.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial (Appendix 1, Table 10) and aquatic habitats (Appendix 1, Table 11) including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g. direct application at a maximum cumulative application

rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risk to Terrestrial Organisms

A risk assessment of tioxazafen and its end-use product formulation MON102133 SC Nematicide Seed Treatment was undertaken for terrestrial organisms based on available toxicity data. A summary of toxicity data is presented in Appendix I, Table 10.

EECs were considered for pollinators, soil dwelling organisms, terrestrial vascular plants, birds and mammals. In Appendix I, Table 12 presents EECs and RQ values for pollinators, and Table 13 to other non-target terrestrial organisms except pollinators, birds and mammals; Table 14 and Table 15 present the estimated daily exposure concentration (EDE) and risk to birds and mammals from treated soybean and corn seeds.

Pollinators: Acute contact for adult honeybees from direct overspray, and acute oral exposure from consumption of tioxazafen-contaminated sucrose solution, did not result in any mortality or any sublethal effects including behavioural abnormalities over the 48-hour observation/exposure period. Tioxazafen is a systemic pesticide which can be distributed in the plant growing from treated seeds. The risk assessment was conducted according to the Guidance for Assessing Pesticide Risks to Bees. This guidance was collaboratively developed by the PMRA, the United States Environmental Protection Agency and the California Department of Pesticide Regulation. The bee adult acute oral LC_{50} value was used in the risk assessment. The maximum consumption rate (nectar forager) was used as a surrogate for other castes of adult bees. At the screening level, the level of concern was exceeded. The risk assessment was further refined based on a residue study indicating that tioxazafen was not detected in pollen and nectar of plants grown from treated seeds. Considering a maximum exposure at the highest limit of detection from study data, and a consumption value determined as above for an adult honeybee, the LOC is not exceeded and it can be concluded that the use of tioxazafen as per label instructions is not expected to pose acute risk to pollinators.

No information was submitted on the chronic and larval toxicity of tioxazafen to pollinators; however, considering that there were no effects on adults at the highest test concentration from both the acute contact and oral routes of exposures, and that no residues in pollen and nectar were detected at a very low LOD (about 2 000 and 475 000 times smaller than the highest test concentrations that resulted in no effects in the oral and contact studies, respectively), the risk to pollinator larvae as well as chronic risk are expected to be negligible.

Another potentially important route of exposure for bees is contact with dusts generated during planting of treated seed. Bees could be exposed to pesticides in dust while in flight (contact exposure), or through flowers where dust has been deposited (contact or dietary exposure). Although the exposure level from this route cannot be reliably quantified, considering that tioxazafen is practically non-toxic to the adult honey bee on a contact basis and that there is no other indicator that dust could be of concern, the risk to pollinators from dust off during planting of treated seeds is expected to be negligible.

Terrestrial plants: The toxic effects of a formulated tioxazafen product (MON102133 EC Nematicide Seed Treatment) on four monocotyledonous and six dicotyledonous plants were tested over 21 days of exposure at a maximum application rate of 0.31 kg a.i./ha (seedling emergence). A significant reduction in plant emergence and survival was observed for a single species (onions, monocotyledonous), and a reduction in shoot height on two species (wheat, monocotyledonous, and cabbage, dicotyledonous). These effects were not observed when the Tier II study was conducted at up to 0.36 kg/ha. Environmental risk of tioxazafen to terrestrial plants was assessed based upon the maximum annual application rate on its related end-use product label, 125 g a.i./ha. This application rate is estimated from planting soybeans treated at the proposed maximum label rate of 0.25 mg a.i./seed and a planting density of 500 000 seeds per hectare. Based on the seedling emergence of plants, the LOC is not exceeded. It can be concluded that the use of tioxazafen as per label instructions is not expected to pose risk to terrestrial plants.

Soil dwelling organisms: Chronic exposure of earthworms to tioxazafen did not cause mortality up to the highest concentration tested, 1 000 mg a.i. / kg_{soil}; however, sub-lethal effects were apparent at all test concentrations: the NOEC for reduction in body weight was 308.6 mg a.i. / kg_{soil}, and the NOEC for reproductive effects could not be determined due to a 16% reduction in the number of juveniles at the lowest treatment concentration of 95.3 mg a.i. / kg_{soil}. At the screening level, environmental risk of tioxazafen to soil dwelling organisms was assessed based upon the maximum annual application rate on its related end-use product label, 125 g a.i./ha, incorporated into the first 15 cm of soil and assuming a soil density of 1.5 g/cm^3. Based on the chronic toxicity to earthworm (survival and weight gain), the risk assessment indicated that the LOC is not exceeded. Although the LOC is not exceeded based on the reproductive effects, uncertainties remain as effects were observed at the lowest concentration tested; nevertheless, considering that the EEC is about 1 700 times lower than the lowest test concentration, it is concluded the use of tioxazafen as per label instructions is not expected to pose risk to soil dwelling organisms.

Birds: Acute oral exposure of tioxazafen to the bobwhite quail caused 50% mortality at the highest dose tested, and signs of toxicity were observed in all treatment groups (NOEL < 580 mg a.i./kg_{bw}). They included ruffled appearance, lethargy, loss of coordination, lower limb weakness, reduced reaction to external stimuli, depression, and reductions in mean body weights and feed consumption. For the canary, the acute oral LD_{50} was 315 mg a.i./kg_{bw}. No treatment-related effects on food consumption or body weights were observed. When tioxazafen was administered in the diet, the resulting LD_{50}s were 835 and 907 mg a.i./kg_{bw}/d for the bobwhite quail and mallard duck, respectively.

Following chronic exposure to tioxazafen, reproductive effects were observed for both the bobwhite quail and the mallard duck at NOELs of 37.85 and 84.86 mg a.i./kg_{bw}/d, respectively. NOELs were based on a reduction of the number of eggs laid, embryo viability and percent hatch relative to the number of eggs set, eggshell thickness, and 14-d survivor weight.

The exposure of birds and mammals to a pesticide through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal, and the number of seeds available for consumption. In the screening level assessment, it is assumed that the diet consists entirely of treated seeds, and all of the treated seed that is planted is available for consumption *ad libitum*, over an extended period of time. Variables of feeding preference, availability of treated seed, or potential avoidance behaviour toward treated seed are not considered at the screening level. Risk to birds from the consumption of treated seeds was assessed based on the label rate of 0.25 mg a.i./seed for soybean and 0.5 mg a.i./seed for corn; risk characterization is presented in Appendix I, Table 14 for soybean and Table 15 for corn. All uses of tioxazafen result in acute, dietary and reproductive risk exceeding the LOC for birds. The risk assessment for birds and mammals was expanded taking into consideration that not all seeds planted will be exposed and available to birds or mammals. The percentage of seeds remaining on the soil surface in field headlands is dependent on the seeding method. This information was used to estimate the numbers of seeds required to reach the selected ecotoxicity endpoint and the area required to find this number of seeds exposed; this refinement does not change the RQ determined.

Acute and reproductive risk concerns to birds at the labelled rate could be triggered through the consumption of as few as 1 to 3 seeds for small birds, 3 to 15 for medium birds and 63-151 for larger birds. Even when precision drilling is used to plant treated seeds, a small bird can find enough exposed seeds on an area as small as 5.4-19 m^2 for soybean and 24-54 m^2 for corn to exceed the acute and reproductive LOC. These areas only consider exposed seeds density and could be significantly reduced if seed found through digging is considered. Medium sized and larger birds need to cover significantly larger areas ranging from 119 to 272m^2 for medium birds and 1193 to 2720m^2 for large birds; based on these data, populations of medium and large birds are not expected to be at risk following the use of tioxazafen. Based on field study data (using bait stations) from Prosser and Hart (2005), and Smith (2006), soybean is not significantly consumed by birds, and birds consume an average of three to 92 corn seeds per visit, with a maximum of 266. In this study, most bird species consuming corn were medium and large birds; a few species of small birds were seldom seen at the baiting station (about 11% of the total number of birds visiting), consuming between one and eleven seeds in a single visit (average: 3-4). The seed consumption data from the field studies represents a worst case scenario for a single feeding because of the high seed availability at the baiting stations. More typical seed densities such as those left on the soil surface after seeding would be expected to attract fewer birds. Feeding rates would also be lower on seeded fields than at feeding stations as birds would take more time to find and move between seeds; however, even considering that it is current practice to use precision drilling for planting corn, the area required for a small bird to forage for enough seeds to reach the endpoints is shown to be small (20 - 30 m^2), and a single seed is sufficient to reach the endpoint; for such a case, the use of the seed consumption data observed at bait stations can be considered a realistic and suitable comparison to the number of seeds required to reach

the avian endpoints. Combined with the information provided in Appendix I, Table 7 and Table 8, it can be concluded that the use of corn seeds treated with tioxazafen is expected to pose acute and reproductive risk of concern to small birds.

To mitigate the risk, directions for use indicating that all treated seeds must be incorporated into soil, leaving no exposed seeds, are required. In addition, a precautionary label statement identifying the toxicity of treated seeds to birds is required on the product label. With the application of these mitigation measures, bird populations are not expected to be at risk and the environmental risk is considered acceptable.

Mammals: The acute oral and reproductive toxicity of tioxazafen to laboratory rats is described in detail in Section 3.1 (Toxicology Summary) of this document. Tioxazafen is practically non-toxic to mammals on an acute basis, with an LD_{50} greater than the highest concentration tested. Based on the label rate and this LD_{50}, the LOC is not exceeded. The resulting acute risk to mammals would be negligible.

No reproductive effects were observed in the chronic mammalian study; therefore, the highest test concentration was considered to be the NOAEL value. Based on the label rate and this NOAEL value, the LOC is exceeded for all uses of tioxazafen. As no reproductive effects were observed in the laboratory studies, there is uncertainty regarding the calculated risk to mammals from chronic exposure to tioxazafen. To mitigate any potential risk resulting from this uncertainty, a precautionary label statement identifying the toxicity of treated seeds to mammals is required on the product label. Directions for use indicating that all treated seeds must be incorporated into soil are also required.

The resulting risk to mammals is expected to be acceptable.

4.2.2 Risk to Aquatic Organisms

Aquatic organisms can be exposed to tioxozafen through run-off. A risk assessment of tioxazafen and its end-use product formulation MON102133 SC Nematicide seed treatment was undertaken for aquatic organisms based on available toxicity data (Appendix I, Table 11): test organisms included the midge larvae, freshwater crustacean, fish (cold and warm water), algae, diatom and macrophyte, and saltwater amphipod, shrimp, oyster, diatom and fish. Studies were conducted with the parent tioxazafen and additional studies were conducted with its isomer MON102130 (the freshwater crustacean, *D. magna*, diatom, *N. peliculosa* and fish, rainbow trout) as well as with the formulated product MON102133 (freshwater fish: rainbow trout). All laboratory studies conducted with tioxazafen, its isomer MON102130 and the formulated product MON102133 SC Nematicide Seed Treatment indicated that they are toxic to aquatic organisms on an acute basis. Following a chronic exposure to tioxazafen of 28 days, mysid shrimps showed no signs of toxicity up to the highest concentration tested, 0.044 mg a.i./L; however, signs of reproductive toxicity were seen on *D. magna* exposed to tioxazafen for 21 days. They included significant reduction in adult survival and number of offspring, with a NOEC of 0.0059 mg a.i./L. Effects of chronic exposure of tioxazafen to fish was assessed with a 33-day early life stage toxicity test. Signs of toxicity included larval survival, weight and total length, with a NOEL of 0.0094 mg a.i./L.

EECs for aquatic environments were estimated through modelling of the combined residue of tioxazafen and its three transformation products 3-thienyl 102100, MON 102100 iminoamide (IMI) and benzamidine (BEN) before Canadian labelled rates were established. A maximum rate of 250 g a.i./ha was considered for water modelling purposes to cover all potential uses. It was further established that the maximum labelled rate for use in Canada would be lower (125 g a.i./ha); the rate used for water modelling purposes being higher than the maximum Canadian labelled rate, risk assessments based on the resulting EECs in water encompass all uses accepted in Canada. The parent and transformation products were modelled considering their transformation relationship in soil and water. The resulting EEC for the parent and that for the transformation products were then added up to calculate the combined residue EEC. In Appendix I, Table 16 presents inputs used to model surface water and sediment pore water concentrations.

For Level 1 aquatic ecoscenario assessment, estimated environmental concentrations (EECs) of the combined residue from runoff into a receiving water body was simulated using the PWC (Pesticide in Water Calculator) model. The PWC model simulates pesticide runoff from a treated field into an adjacent water body and the fate of the pesticide within that water body. For the Level 1 assessment, the water body consists of a 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha. A seasonal water body was also used to assess the risk to amphibians. This water body is a scaled-down version of the permanent water body noted above, but having a water depth of 0.15 m. In addition to EECs in overlying water, pore water concentrations were also simulated, for use in the aquatic risk assessment for sediment-dwelling organisms.

Five standard regional scenarios, i.e., Raspberry in British Columbia, Potato in Manitoba and Prince-Edward Island, and Corn in Ontario and Quebec, were modelled to represent different regions of Canada. A number of initial application dates between April and June were modelled for each scenario. The EECs are for the portion of the pesticide that enters the water body via runoff only; deposition from spray drift is not included. The model was run for 50 years for all scenarios. For each year of the simulation, PWC calculates peak (or daily maximum) and time-averaged concentrations. For risk assessment purposes, the maximum peak concentration was used. In Appendix 1, Table 17 presents the largest modelled aquatic EECs and the risk assessment to non-target aquatic and sediment-dwelling organisms.

The risk assessment indicated that the RQ values for acute, chronic and reproductive toxicity to representative species of freshwater invertebrates, algae, diatoms, fish and sediment-dwelling organisms, and marine invertebrates and fish, did not exceed the LOC. Considering that the LOC was not exceeded for any species at a rate of 250 g a.i./ha, which is higher than the maximum labelled rate of 125 g a.i./ha that was further established, a risk assessment at the labelled rate is not required.

5.0 Value

5.1 Consideration of Benefits

Nematode infestations result in root dysfunction which leads to crop yield losses. The relative damage from nematodes is largely associated with their population density in the soil. Presently, traditional fumigant and non-fumigant nematicides are not commonly recommended for nematode management in either soybean or field corn productions since the costs for these materials often do not make it cost effective for treatment. Applying a nematicide via seed treatment application would make the chemical control of nematodes more economical and practical.

Currently, there are only two biological seed treatment products registered in Canada to suppress certain nematodes in either field corn or soybean. Refer to Appendix I, Table 19 for further information on alternative products. The registration of MON 102133 SC Nematicide Seed Treatment would provide Canadian growers with the only conventional seed treatment product to manage nematode infestation on soybean and field corn.

No resistance information is available for active ingredient tioxazafen. The probability of nematode resistance arising from the labelled use of MON 102133 is very low since it is limited to a single pre-planting application.

5.2 Effectiveness Against Pests

Efficacy data from twenty-six trials and scientific rationales were submitted to support use claims against three soil-inhabiting nematodes in soybean, including soybean cyst nematode, root lesion nematode and root knot nematode. Efficacy data from twenty-six trials and scientific rationales were submitted to support use claims against seven soil-inhabiting nematodes in field corn, including root knot nematode, cyst nematode, dagger nematode, root lesion nematode, pin nematode, spiral nematode and stunt nematode. Although high variation in nematode populations was observed in certain trials, data and rationales demonstrated the efficacy of MON 102133 in suppressing listed nematodes in both soybean and field corn, as compared to the commercial standard when such treatments were included in the efficacy trials. Based on the value information for these specific uses, the use claims are supported.

5.3 Non-Safety Adverse Effects

There have been no adverse effects to either soybean or field corn evaluated in trials conducted at proposed rates for MON 102133. No phytotoxicity or crop injury was reported.

5.4 Supported Uses

Use claims of MON 102133 SC Nematicide Seed Treatment for suppression of listed nematodes in soybean and field corn are supported according to the use directions provided. Details of the supported uses are provided in Appendix I, Table 20.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, tioxazafen and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Tioxazafen does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 18 for comparison with Track 1 criteria.

- Transformation products do not meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *PMRA Formulants Policy.*

- The end-use product, MON 102133 SC Nematicide Seed Treatment, contains the preservative 1,2-benzisothiazoline-3-one which contains low levels of dioxins and furans. These are being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP.

- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

7.0 Summary

7.1 Human Health and Safety

The toxicology database for tioxazafen is adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies on laboratory animals, the primary targets were the adrenal glands and the liver. In rats, a common but non-adverse finding was hyperostosis of the femur. Hyperplasia was noted at the site of contact following repeated dermal and inhalation exposures. There was no indication of increased susceptibility of the young in reproduction or developmental toxicity studies. There was no effect on reproductive performance or outcome. Tioxazafen showed signs of dysregulation of the immunologic response. There was no evidence that tioxazafen was selectively neurotoxic. Tioxazafen did not damage genetic material. There was evidence of oncogenicity after long-term oral dosing in rodents as demonstrated by increased incidences of hepatocellular carcinomas and systemic hemangiosarcomas in male mice. Benign endometrial polyps (equivocal evidence) and hibernomas were noted in female rats. Hibernomas (equivocal evidence) were also observed in male rats. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Workers treating seed with MON 102133 SC Nematicide Seed Treatment and workers planting treated seed are not expected to be exposed to levels of tioxazafen that will result in health risks of concern risk when MON 102133 SC Nematicide Seed Treatment is used according to label directions. The personal protective equipment and engineering controls on the product label are adequate to protect workers.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is tioxazafen and the metabolite benzamidine in plant products and in animal matrices. The proposed use of tioxazafen on field corn and soybean and the importation of treated cotton does not constitute a health risk of concern for chronic or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs.

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[9] DIR2006-02, *PMRA Formulants Policy*.

7.2 Environmental Risk

Tioxazafen is slightly persistent to persistent in the terrestrial environment. Tioxazafen residues in soil may carry over to the following growing season. Tioxazafen is relatively immobile in soil and has a limited potential to leach to groundwater. It may enter aquatic environments through surface runoff. In aquatic environments, tioxazafen is non-persistent and will partition to both the water and sediment layers. The use of tioxazafen is not expected to pose a risk to aquatic organisms. Tioxazafen is not expected to pose a risk to most non-target terrestrial organisms, with the exception of birds and small wild mammals. Label statements indicating the toxicity of tioxazafen to birds and mammals are required along with label directions indicating that all exposed seeds must be removed or incorporated into soil. With the application of these mitigation measures, the environmental risk from the use of treated seed treated with tioxazafen is considered acceptable.

Toxic substance management policy considerations:
Tioxazafen and its major soil and aquatic transformation products do not meet all the TSMP criteria for a Track 1 substance.

7.3 Value

The active ingredient of MON 102133 SC Nematicide Seed Treatment, tioxazafen, has been demonstrated to be effective against certain soil-inhabiting nematodes in field corn and soybean, including economically important ones such as the soybean cyst nematode. It suppresses various nematodes during the seedling stage of the growing season, which can result in higher crop yields to growers. The registration of MON 102133 SC Nematicide Seed Treatment provides Canadian growers with a conventional seed treatment product to suppress nematode infestation on field corn and soybean. The product can also be applied in combination with certain fungicide and insecticide seed treatments.

Based on the value information provided, the registration of MON 102133 SC Nematicide Seed Treatment to suppress listed nematodes in soybean and field corn is supported.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of MON 102100 Technical and MON 102133 SC Nematicide Seed Treatment, containing the technical grade active ingredient Tioxazafen, to suppress certain soil-inhabiting nematodes in field corn and soybeans.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
ER_{25}	effective rate for 25% of the population
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RSD	relative standard deviation
SC	suspension concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis (Soil and Water)

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	AG-ME-1636	MON 102100	GC-MS/MS	0.0050 ppm	2483497
		Benzamidine	LC-MS/MS	0.0013 ppm	2483128
Water	EPL-BAS-115G761A	MON 102100	LC-MS/MS	0.1 µg/L	2483184
		Benzamidine	LC-MS/MS	0.1 µg/L	2483125
		MON 102130	LC-MS/MS	0.1 µg/L	
Plant	115G806A	Tioxazafen Benzamidine[1]	ESI LC-MS/MS (enforcement)	0.01 ppm per analyte (i.e., as tioxazafen and benazamidine *per se*)	2483129 + 2483126
	ME-1604	Tioxazafen	EI GC-MS/MS (data gathering)	0.0025	2483115 Note: The protocol for Method AG-ME-1604-03 (Dated August 22, 2014) is in Appendix II.
	ME-1579	Benzamidine[1]	ESI LC-MS/MS (data gathering)	0.0025 (Tioxazafen equivalents)	2483115 Note: The protocol for Method ME-1579-02 (Dated August 22, 2014) is in Appendix III.
Animal	ME-1764[3]	Tioxazafen	EI GC-MS/MS Tioxazafen + benzonitrile LC-MS/MS Benzamidine + 2-thenoylglycine (data gathering and enforcement)	0.01 (Tioxazafen equivalents) 0.025 (Tioxazafen equivalents; fat) 0.01 (Tioxazafen equivalents; milk); 0.025 (Tioxazafen equivalents; kidney); 0.06[4] (Tioxazafen equivalents; liver)	2483127 + 2483130 + 2483123

[1] Chemical name: benzenecarboximidamide.
[2] Chemical name: *N*-(2-thienylcarbonyl)glycine
[3] Previously identified as AG-ME-1764.
[4] The LOQ for 2-thenoylglycine (as tioxazafen equivalents) in liver was modified from 0.01 ppm to 0.06 ppm during in-study validation due to matrix interference (PMRA No. 2483123).

Table 2 Toxicity Profile of MON 102133 SC Nematicide Seed Treatment, containing TIOXAZAFEN

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type /Animal/PMRA #	Study Results
Acute oral toxicity Rat (Sprague-Dawley) PMRA #2483132	LD_{50}, ♀ ≥ 5000 mg/kg bw Low toxicity Clinical signs included: hypoactivity, irregular respiration, yellow staining in litter, facial staining, reduced fecal volume.
Acute dermal toxicity Rat (Sprague-Dawley) PMRA #2483133	LD_{50} ≥ 5000 mg/kg bw Low toxicity Clinical signs included dermal irritation at test site.
Acute inhalation toxicity (nose-only) Rat (Sprague-Dawley) PMRA #2483134	LC_{50} ≥ 5.06 mg/mL Low toxicity Clinical signs included irregular respiration, body weight loss (day 1), alopecia.
Dermal irritation Rabbit (New Zealand White) PMRA #2483136	MAS = 1.2 MIS = 1.7 (at 24 hours) Slightly irritating All scores 0 by day 7.
Eye irritation Rabbit (New Zealand White) PMRA #2483135	MAS = 0 MIS = 0 Non-irritating
Dermal sensitization (Buehler test) Guinea Pig (Hartley) PMRA #2483137	Negative
Bacterial reverse mutation *S. typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. Coli* WP2uvrA PMRA#2483500	Negative Tested up to precipitating concentrations.
In vivo micronucleus assay (gavage) Mouse (CD-1) PMRA#2483512	Positive at 1500 mg/kg bw/day (24 hour harvest). Dose range-finding: ≥ 1000 mg/kg bw: piloerection ≥ 2000 mg/kg bw: lethargy, death Main test: 1500 mg/kg bw(♂): piloerection, lethargy

Table 3 Toxicity Profile of Technical TIOXAZAFEN

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Effects seen above, as well as non-adverse effects noted below, the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/ Animal/PMRA #	Study Results
Toxicokinetics Sprague-Dawley rat PMRA# 2483488, 2575984	Sprague Dawley rats were administered [phenyl-UL-^{14}C]-MON 102100 (PH radiolabel) or [thiophene-2-^{14}C]-MON 102100 (TH radiolabel) (98.2-99.9% a.i.) intravenously or by oral gavage at dose levels of 3 mg/kg bw or 100 mg/kg bw. The toxicokinetic phase consisted of six groups, each with 8 ♂ rats/group; single IV dose at 3 mg/kg bw or single oral dose at 3 or 100 mg/kg bw. The disposition and metabolite identification phase consisted of twelve groups, each with 4 ♂/group, with three groups also having 4 ♀/group. The ♂ received a single IV dose at 3 mg/kg bw, a single oral dose at either 3 or 100 mg/kg bw, or a daily oral dose of non-labeled TIOXAZAFEN at 3 mg/kg bw for 14 days followed by a single radiolabeled dose at 3 mg/kg bw. Bile duct-cannulated ♂ received a single oral dose at 100 mg/kg bw. A single oral dose at 3 mg/kg bw was administered to ♀. The quantitative whole body autoradiography phase consisted of four groups, each with 4 rats/sex/group; rats received a single oral dose at 3 or 100 mg/kg bw. **Absorption:** The maximum plasma concentration was at 2 hours (3 mg/kg bw) or 4 hours (100 mg/kg bw) post-dosing. The bioavailability of the PH-radiolabeled compound was 57.5% (low dose) and 121% (high dose). The bioavailability of the TH-radiolabeled compound was 72.7% (low dose) and 95.1% (high dose). Based on excretion in urine and bile up to 48 hours post-dosing, absorption of a high oral dose was approximately 77-81%. **Distribution:** A total of <1% of the administered dose (AD) remained in animal tissues and organs at 7 days post-dosing, with highest levels in the adrenal glands, kidneys, liver, and thyroid. Highest and longest lasting radioactivity levels at T_{max} and 48 hours post-dosing were in the liver, kidney, and renal cortex. The adrenal glands also had high radioactivity levels at T_{max}, which continued to increase at 48 hours post-dosing. Radioactivity in the adrenals was 2-fold higher in ♀, and in the stomach was 5-fold higher in ♂ at T_{max}. In the urinary bladder, radioactivity at T_{max} was 25-fold higher when dosed with the PH radiolabel at 100 mg/kg bw compared to the TH radiolabel. **Metabolism:** TIOXAZAFEN was extensively metabolized. Unchanged TIOXAZAFEN was not detected in any of the excreta samples. A total of 73 metabolites were identified (most <1% of the AD). In the urine, benzamidine was recovered at 4-13% of AD (PH radiolabel), 5-hydroxy TIOXAZAFEN glucuronide was recovered at 1-5% of AD (both radiolabeled compounds), hippuric acid at 1-3% of AD (PH radiolabel), and thenoylglycine at 0.7-6% of AD (TH radiolabel). The uncharacterized metabolites M26 and M29 were also quantitatively high in the urine for both radiolabels, with a recovery of 0.2-4% and 0.4-3% of AD, respectively. In the feces, benzamidine was recovered at 9-26% of AD

Study Type/ Animal/PMRA #	Study Results
	(PH radiolabel) and unknown metabolite M39 was recovered at 5-9% (PH radiolabel) and 8-17% (TH radiolabel) of AD. The following metabolites were recovered in the bile of animals dosed with the PH radiolabel compound (% dose): dihydroxy TIOXAZAFEN glucoside sulfate (2%), dihydroxy TIOXAZAFEN diglucuronide (3%), butenoic acid sulfonate glutathione (3%), and 5-hydroxy TIOXAZAFEN glucuronide (27%). Animals dosed with the TH-radiolabel compound had the following metabolites recovered in the bile: butenoic acid sulfonate glutathione (2%), 5-hydroxy iminoamide glucuronide (2%) and 5-hydroxy TIOXAZAFEN glucuronide (23%). **Excretion:** The half-life of elimination from plasma was 44–47 hours and 38–42 hours for low and high dose, respectively. Overall, 45-69% of AD was excreted in feces and 24-38% of AD was excreted in urine. It was determined in a pilot phase that there was very low excretion (≤0.6%) in expired air. The greatest amount of radioactivity recovered in the urine was 0-12 hours post-dosing, with little elimination after 24 hours. The greatest amount of radioactivity recovered in the feces was 12-24 hours post-dosing, with significant amounts still being excreted in the 24–48 hour collection period. Total recovery in bile duct-cannulated animals dosed with the PH radiolabel was 85% (21% urine, 3% feces, 60% bile) and those dosed with the TH radiolabel was 89% (45% urine, 11% feces, 32% bile). Overall, there were no significant differences in metabolism with respect to the position of the radiolabel, sex, dosing route, duration, or dose level. **Major proposed pathways:** 1. Reductive cleavage of the N-O bond of the oxadiazole ring leading to MON 102100 Iminoamide, a transient metabolite that is not observed as a free metabolite in any matrix. The iminoamide metabolite is hydrolyzed (almost certainly enzyme-mediated) to benzamidine, the major urine and fecal metabolite, which is also further hydrolyzed to benzoic acid (eliminated in urine as the glycine conjugate, hippuric acid). Hydrolysis of the iminoamide also gives 2-thiophenecarboxylic acid (eliminated in urine as the glycine conjugate, 2-thenoylglycine). 2. Hydroxylation of the thiophene ring (primarily at the 5-position of the ring, adjacent to the sulfur atom) and conjugation as the glucuronide (major) or sulfate.
Acute oral toxicity Rat (Sprague-Dawley) PMRA #2483491	LD_{50} > 5000 mg/kg bw Low toxicity No clinical signs of toxicity observed.
Acute dermal toxicity Rat (Sprague-Dawley) PMRA#2483490	LD_{50} > 5000 mg/kg bw Low toxicity Clinical signs included ocular and/or nasal discharge (♂/♀); dermal irritation at dose site (♂); anogenital staining, bw loss (week 1)(♀).
Acute inhalation toxicity Rat (Sprague-Dawley) PMRA#2493774	LC_{50} > 5.21 mg/mL Low toxicity Clinical signs included irregular respiration, bw loss (day 1)(♂/♀).

Study Type/ Animal/PMRA #	Study Results
Eye irritation Rabbit (New Zealand White) PMRA#2483582	MAS = 2 MIS = 47 (1 hour) Minimally irritating All scores 0 by day 7.
Dermal irritation Rabbit (New Zealand White) PMRA #2483583	MAS = 0 MIS = 0 Non-irritating
Dermal sensitization (Buehler) Guinea Pig (Hartley) PMRA#2483508	Negative
28-day oral (dietary) Mouse (CD-1) PMRA#2483477	NOAEL = 58/70 mg/kg bw/day (♂/♀) LOAEL = 184/219 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ fc and fe (days 0-3), ↑ bilirubin, ↑ liver wt, centrilobular hepatocellular hypertrophy (♂and♀); ↓ bwg (days 0-3) (♂); ↓ defecation, bw loss (days 0-3), death (1 ♀ sacrificed in extremis on day 5. Signs included: bw loss, intermittent tremors, pale body and extremities, dermal atonia, thin appearance, partial closure of eyes, ↓ defecation, hepatocellular single cell necrosis), ↑ cholesterol, ↑ GGT (♀)
90-day oral (dietary) Mouse (CD-1) PMRA#2483480	NOAEL = 259 mg/kg bw/day (♂) LOAEL = Not established (♂) No adverse effects were observed in males. NOAEL = 174 mg/kg bw/day (♀) LOAEL = 319 mg/kg bw/day (♀) Effects at the LOAEL (♀): death (1 ♀ sacrificed in extremis day 3; signs included: partial closure of eyes, dermal atonia, body cool to touch hypoactivity, hepatocellular necrosis, hepatocellular hypertrophy, thymic cortical lymphoid necrosis), ↓ bw/bwg, ↓ fc, ↓ fe (week 1), ↑ bilirubin, ↑ cholesterol, ↑ liver wt, hepatocellular hypertrophy.
28-day oral (dietary) Rat (Sprague-Dawley) PMRA#2483478	NOAEL = 15/18 mg/kg bw/day (♂/♀) LOAEL = 76/89 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ bw/bwg, metaphyseal hyperostosis in femur (♂/♀); ↓ fc, ↑ adipose tissue in bone marrow of sternum (♂).
90-day oral (dietary) Rat (Sprague-Dawley) PMRA #2483481	NOAEL = 47 mg/kg bw/day (♂) LOAEL = 91 mg/kg bw/day (♂) Effects at the LOAEL (♂): ↓ bw/bwg, ↓ fc, ↑ cholesterol, ↑ rel liver wt, ↓ urine pH, ↑ rel kidney wt , brown pigmented kidneys, metaphyseal hyperostosis in femur, foreign material in cortical tubular lamina of kidney NOAEL = 19 mg/kg bw/day (♀) LOAEL = 55 mg/kg bw/day (♀) Effects at the LOAEL (♀): ↓ bw/bwg, variable urine colour, metaphyseal hyperostosis in femur

Study Type/ Animal/PMRA #	Study Results
28-day oral (capsule) Dog (Beagle) PMRA#2483475	NOAEL and LOAEL not established as study was considered supplemental. Effects at ≥100 mg/kg bw/day: soft feces, feces containing white/red material, emesis; ↓ GGT (♂); ↓ total protein, ↓albumin, ↓ thymus wt, single cell necrosis in thymus in 1 ♀ at 100 and 1 ♀ at 500 mg/kg bw/day (♀) Effects at ≥250 mg/kg bw/day: ↓ defecation, red mucoid feces, diarrhea, ↓ bwg/ bw loss, ↓fc, ↓ A/G ratio, ↓ total bilirubin, ↓AST, ↓ALP; ↑eosinophils, ↑ BUN, ↓ total protein, ↓albumin (♂); emesis containing red material, dermal atonia, ↓ activity and thin appearance in 1♀, ↑WBC, ↑neutrophils, ↑monocytes, ↑platelets, ↓ ALT, ↓GGT, ↓ heart wt, lymphoid depletion in thymus (♀) Effects at 500 mg/kg bw/day: One ♀ sacrificed in extremis on day 16 due to excessive clinical signs of toxicity (all remaining animals also sacrificed on day 16), ↓calcium, ↑triglycerides, ↑BUN, edema of the mesentery and/or pancreas, clear fluid in abdominal cavity, ↑hepatocellular glycogen; ↑WBC, ↑monocytes, ↑neutrophils, ↓ ALT, ↓epididymides, ↓prostate, ↓testes, ↓thymus wt (♂); ↑glucose, ↑chloride ↓phosphorus (♀)
90-day oral (capsule) Dog (Beagle) PMRA#2483482	NOAEL = 40 mg/kg bw/day (♀) LOAEL = 120 mg/kg bw/day (♀) Effects at the LOAEL (♀): red and/or white material in feces, death (1 ♀ day 3; relationship to treatment considered equivocal) NOAEL = 120 mg/kg bw/day (♂) LOAEL = Not established (♂) No adverse effects were observed in males.
28-day dermal Rat (Sprague-Dawley) PMRA# 2483487	NOAEL = Not established LOAEL = 100 mg/kg bw/day Effects at the LOAEL: epidermal hyperplasia (♂and♀); vacuolation of adrenal cortex (↑ incidence and severity)(♂)
28-day inhalation Rat (Sprague-Dawley) PMRA#2483471	NOAEC = 15 mg/m^3 (3.9 mg/kg bw/day) LOAEC = 50 mg/m^3 (13 mg/kg bw/day) Effects at the LOAEC: red/purple/yellow material on various body surfaces,↓ bw, ↓ bwg, ↓ fc (♂and♀); ↑ bilirubin, sub-acute inflammation of nasal passages, degeneration/squamous metaplasia of the respiratory epithelium, exudate in nasal passages (♂); ↑cholesterol, atrophy and vacuolation of the adrenal cortex (♀)
90-day inhalation Rat (Sprague-Dawley) PMRA#2483467	NOAEC = 15 mg/m^3 (3.9 mg/kg bw/day) LOAEC = 50 mg/m^3 (13 mg/kg bw/day) Effects at the LOAEC: red coloured urine, ↑ urobilinogen, vacuolation of the adrenal cortex, ↑ severity of hyperplasia of the respiratory epithelium, lymphoid hyperplasia of the nasal cavity (♂); dried purple material on urogenital area and ventral trunk, ↑ incidence of hyperplasia of the respiratory epithelium lymphocyte infiltrate in the nasal cavity (♀)
18-month oncogenicity (dietary) Mouse (CD-1) PMRA#2483505	NOAEL = 41 mg/kg bw/day (♂) LOAEL = 120 mg/kg bw/day (♂) Effects at the LOAEL: ↑ hepatocellular hypertrophy, ↑ incidence and/or severity of pigmented macrophages, scattered necrotic hepatocytes (♂) NOAEL = 10 mg/kg bw/day (♀) LOAEL = 50 mg/kg bw/day (♀)

Study Type/ Animal/PMRA #	Study Results
	Effects at the LOAEL: ↑ hepatocellular hypertrophy, ↑ incidence and/or severity of pigmented macrophages, scattered necrotic hepatocytes. Tumours in ♂ Hepatocellular adenomas: 4, 2, 7, 2, 4, 6 (8%, 4%, 14%, 4%, 8%, 12%) Hepatocellular carcinomas: 0, 1, 2, 0, 2, 6 (0%, 2%, 4%, 0%, 4%, 12%) Combined adenomas/carcinomas: 4, 3, 7, 2, 6, 9 (4%, 6%, 14%, 4%, 12%, 18%) Systemic hemangiosarcomas: 2, --, --, 0, 2, 6 (-- data not presented) (4%, --, --, 0%, 4%, 12%) **Evidence of carcinogenicity: Increased incidence of hepatocellular carcinomas and hemangiosarcomas in males at the high dose level.**
Two-year combined chronic toxicity/oncogenicity (dietary) Rat (Sprague-Dawley) PMRA#2483469	NOAEL = 4/5 mg/kg bw/day (♂/♀) LOAEL = 13/16 mg/kg bw/day (♂/♀) Effects at the LOAEL: foreign material in the kidneys (♂and♀); ↓ bwg (week 1), ↑ liver wt, hibernomas (equivocal)(♂); endometrial stromal tumours (polyps) (equivocal)(♀). Tumours in ♂ (incidence/# tissues examined) Hibernomas: 4, 1, 4, 4, 8, 5 (4/4, 1/1, 4/4, 4/5, 8/9, 5/5) Tumours in ♀ (incidence/# tissues examined) Hibernomas: 2, 3, 6, 3, 3, 9 (2/3, 3/3, 6/6, 3/3, 3/3, 9/9) Endometrial polyps: 0, --, 0, 3, 6*, 5 (0/52, 0/0, 0/2, 3/52, 6*/52, 5/52) * Statistically significant ($p<0.05$) **Evidence of carcinogenicity: Endometrial polyps in females at ≥16 mg/kg bw/day considered equivocal. Hibernomas (brown fat tumours) in the thoracic cavity of males at ≥ 13 mg/kg bw/day considered equivocal. Hibernomas in females at the highest dose level of 48 mg/kg bw/day.**
Two-generation reproduction (dietary) Rat (Sprague-Dawley) PMRA#2483486	Parental NOAEL = 5 mg/kg bw/day (♂) Parental LOAEL = 20 mg/kg bw/day (♂) Effects at the parental LOAEL (♂): ↑ rel. liver wt (P/F_1), foreign material in cortical tubular lamina of kidney (P/F_1), ↑ adrenal wt (F_1), adrenocortical vacuolation (P/F_1) Parental NOAEL = 20 mg/kg bw/day (♀) Parental LOAEL = 60 mg/kg bw/day (♀) Effects at the parental LOAEL (♀): ↓ fc (P gestation), ↓ bwg (P gestation), ↓ abs adrenal wt (P/F_1), ↑ rel. kidney wt (P) Reproductive NOAEL = 60 mg/kg bw/day Reproductive LOAEL = Not established (no effects noted) Offspring NOAEL = 60 mg/kg bw/day Offspring LOAEL = Not established (no effects noted) No evidence of sensitivity of the young.

Study Type/ Animal/PMRA #	Study Results
Developmental toxicity (gavage) Rat (Sprague-Dawley) PMRA#2483495	Maternal NOAEL = 50 mg/kg bw/day Maternal LOAEL = 200 mg/kg bw/day Effects at the maternal LOAEL: ↑ hair loss, ↓ bw/bwg, bw loss, ↓ fc, ↓ abs adrenal wt Developmental NOAEL = 200 mg/kg bw/day Developmental LOAEL = Not established (no effects noted) No evidence of sensitivity of the young.
Developmental toxicity (gavage) Rabbit (New Zealand White) PMRA#2483494	Maternal NOAEL = 100 mg/kg bw/day Maternal LOAEL = Not established Range-finding study indicated bw loss, ↓ bwg, ↓ fc at ≥100 mg/kg bw/day. Selected doses for main study based on range-finding results. Developmental NOAEL = 100 mg/kg bw/day Developmental LOAEL = Not established (no effects noted) No evidence of sensitivity of the young.
28-day immunotoxicity (dietary) Mouse (CD-1) PMRA#2483476	NOAEL = 80 mg/kg bw/day LOAEL = 240 mg/kg bw/day Effects at the LOAEL: ↑ bilirubin, ↑ liver wt, hepatocellular hypertrophy, ↓ serum IgM response Indication of perturbation/dysregulation of the immunologic response.
Acute oral neurotoxicity (gavage) Rat (Sprague-Dawley) PMRA#2483493	NOAEL = Not established LOAEL = 250 mg/kg bw/day Effects at the LOAEL: ↓ total motor and ambulatory activity counts on day 0 (♂and♀); ↓ defecation, small feces, ↓ body temperature day 0 (♀) No neuropathological findings observed.
90-day oral neurotoxicity (dietary) Rat (Sprague-Dawley) PMRA#2483479	NOAEL = 67 mg/kg bw/day (♂) LOAEL = Not established (♂) No adverse effects were observed in males. NOAEL = 8 mg/kg bw/day (♀) LOAEL = 24 mg/kg bw/day (♀) Effects at the LOAEL (♀): ↓ bw/bwg, ↓ fc No neuropathological findings observed.
Bacterial reverse mutation *S. typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. Coli* WP2uvrA PMRA#2483501	Negative Tested up to the limit concentration.

Study Type/ Animal/PMRA #	Study Results
In vitro mammalian gene mutation assay Chinese hamster ovary cells PMRA#2483503	Negative Tested up to cytotoxic and precipitating concentrations.
In vitro chromosome aberration assay Human lymphocyte cells PMRA#2483504	Negative Tested to cytotoxic and precipitating concentrations.
In vivo micronucleus assay (gavage) Mouse (CD-1) PMRA#2483513	Negative. Effects at 500 mg/kg bw/day: hunched posture, rough haircoat, slight hypoactivity, squinted eyes (♂and♀). Effects at ≥1500 mg/kg bw/day (♀): death (day 1)
Immuno-histochemical staining of tissues from repeat-dose studies Mouse (CD-1) PMRA#2483532	Immuno-histochemical staining of tissues from existing 28-day oral (PMRA# 2483477) and 90-day oral (PMRA# 2483480) mouse studies to examine liver cell proliferation (Ki67 antibody) and peroxisome proliferation (PMP70 and catalase antibodies) using 2-dimensional morphometric analysis. No evidence of increased cell proliferation in the liver (both sexes, all doses; 28- and 90-day mouse studies) or peroxisome proliferation in the liver (both sexes, high dose only; 90-day mouse study). One high-dose female in the 90-day mouse study was euthanized in extremis on day 3, cause of death reported as liver necrosis. This animal exhibited increased Ki67 staining, approximately 24 times higher than the mean of the remaining animals in this group. Cellular proliferation was reported as a regenerative response to the liver necrosis.
In vivo mouse study - CAR/PXR (4- or 14-day dietary) Mouse (CD-1) PMRA#2483514	Clinical pathology and histology evaluations, with immuno-histochemical, enzyme and gene expression profiling relating to a CAR/PXR mouse liver tumour formation MOA. High-dose males exhibited hepatocellular proliferation on day 4. TIOXAZAFEN was a weak inducer of CYP450 (AhR, PPARα, and/or CAR/PXR). There was no effect on glutathione levels.

Table 4 Toxicity Profile of Metabolite MON 102130 (photolyte of TIOXAZAFEN)
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Rat (Sprague-Dawley) PMRA #2483120	LD_{50} ♀ ≥ 5000 mg/kg bw Low toxicity Clinical signs included: death (2♀), hypoactivity, irregular respiration, hunched posture, reduced fecal volume, soft feces and/or anogenital staining, distension of the stomach and intestines.
28-day oral toxicity (dietary) Rat (Sprague-Dawley) PMRA#2483131	NOAEL = 15/16 mg/kg bw/day (♂/♀) LOAEL = 72/77 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ HGB, ↓ HCT, ↑ albumin, ↑ globulin, ↑ total protein, ↑ liver wt, ↑ incidence of centrilobular hepatocellular hypertrophy (♂/♀); ↑ rel spleen wt (♂); ↓ bwg (wk 1), ↓ fc (wk 1), ↑ bilirubin, ↑ cholesterol , ↑ rel kidney

Study Type/Animal/PMRA #	Study Results
	wt (♀)
Bacterial reverse mutation *S. typhimurium* strains TA98, TA100, TA1535 and TA1537; *E. Coli* WP2uvrA PMRA #2483499	Negative Tested up to precipitating concentrations.
In vivo micronucleus assay (gavage) Mouse (CD-1) PMRA #2483511	Negative Initial range finding (corn oil): ≥ 500 mg/kg bw: death (all animals); piloerection (♂); prostration and piloerection (1 ♀; all others dead) Repeat range-finding (corn oil): 200 mg/kg bw: piloerection 300 mg/kg bw: piloerection, lethargy; death (♂); diarrhea (♀) 400 mg/kg bw: death (all animals); piloerection (♂) Additional range-finding (CMC): ≥ 500 mg/kg bw: piloerection (♂) Initial main test (corn oil): 200 mg/kg bw (♂): piloerection, diarrhea 300 mg/kg bw (♀): piloerection, lethargy, diarrhea, prostration Additional main test (CMC): ≥ 500 mg/kg bw(♂): piloerection

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for TIOXAZAFEN

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary	Acute oral neurotoxicity study in rats	LOAEL = 250 mg/kg bw Decreased total motor and ambulatory activity counts	300[2]
	ARfD = 0.8 mg/kg bw		
Repeated dietary	Two-generation reproductive toxicity study in rats	Parental NOAEL = 5 mg/kg bw/day Increased adrenal weight and adrenocortical vacuolation	100
	ADI = 0.05 mg/kg bw/day		
Short-term and Intermediate-term dermal	28-day dermal toxicity study in rats	LOAEL = 100 mg/kg bw/day Epidermal hyperplasia and adrenocortical vacuolation	300[2]
Short-term and Intermediate-term inhalation	Combined results of the 28-day and 90-day inhalation toxicity studies in rats	NOAEC = 15 mg/m^3 (3.9 mg/kg bw/day) Decreased body weight; adrenocortical vacuolation and atrophy	100

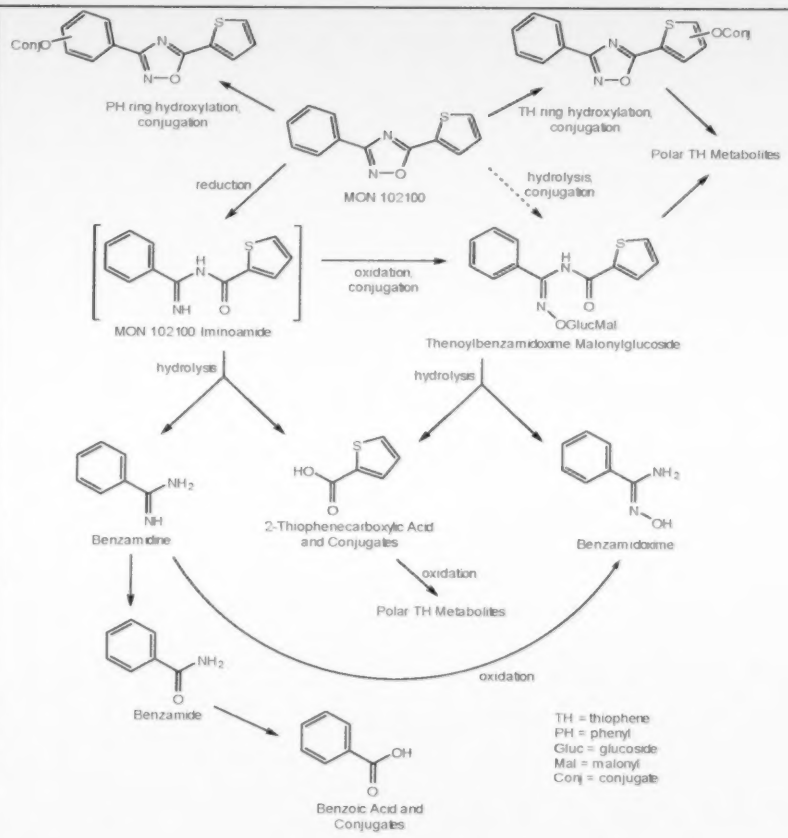
Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Cancer	Low dose linear extrapolation approach [q_1^* = 3.41 × 10^{-3} (mg/kg bw/day)$^{-1}$] for hemangiosarcomas in male mice. Equivocal evidence of increased endometrial stromal tumours (polyps) in female rats; equivocal evidence of thoracic cavity hibernomas in male rats; increased incidence of thoracic cavity hibernomas in female rats; increased incidence of hepatocellular carcinomas and hemangiosarcomas in male mice. Endpoints selected for the non-cancer risk assessment are protective of these findings.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments
[2] for use of a LOAEL

Table 6 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN CORN			PMRA # 2483578
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen (PH-label); [oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen (TH-label)		
Test Site	The treated corn seeds (*Zea mays* L.; Dekalb® DKC69-71, a Roundup® Corn 2/YieldGuard® corn borer variety which is tolerant to glyphosate and acetolactate synthase inhibitor herbicides) were planted outdoors in a loamy sand soil in 16 ft^2 plastic-lined wooden boxes.		
Treatment	The solid radiolabeled tioxazafen test substances were separately formulated as aqueous suspension concentrates by wet-milling to a very small particle size, and applied as seed coatings to untreated seed together with Acceleron® fungicide/insecticide seed treatment formulation. The Acceleron® formulation was prepared using a seed colorant, finishing polymer, insecticide (clothianidin) and fungicide (metalaxyl, ipconazole and trifloxystrobin).		
Total Rate	Target: 1.0 mg a.i./seed [0.24 kg a.i./ha*] Actual: PH-label: 1.09 mg a.i./ seed [0.26 kg a.i./ha] TH-label: 1.28 mg a.i./ seed [0.30 kg a.i./ha] *Based on a seeding rate of 35 seeds/plot and 1.0 mg tioxazafen per seed.		
Formulation	Aqueous suspension concentrate.		
Preharvest interval	Immature foliage samples were collected as thinnings 24 days after planting (24-DAP). Forage samples were collected 101-DAP at the late dough/early dent stage. Mature stover and mature grain were collected 130-DAP.		
Matrices	PHI (DAP)	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
		TRRs (ppm)	TRRs (ppm)
Corn thinnings	24	1.719	1.967
Corn forage	101	0.0148	0.0084
Corn stover	130	0.0644	0.0415
Corn grain	130	0.0012	0.0020
Total radioactive residues (TRRs) were determined by direct combustion and liquid scintillation counting (LSC), and were expressed as tioxazafen equivalents. ^{14}C-Residues were <0.0001 ppm in all control samples of corn thinnings, forage, stover and grain. Corn matrices were subjected to an exhaustive extraction procedure involving four extractions with acetone/water [80:20, v/v (3x) and 40:60,vv/v (1x) for thinnings and 40:60, v/v (4x) for forage, stover and grain]. Metabolites of tioxazafen in corn foliage matrices were based on high performance liquid chromatography (HPLC) analysis of the acetone/water extracts with reference standards, and the identity of metabolites was confirmed by thin layer chromatography (TLC). Corn grain extracts were not analyzed by			

HPLC because the levels of extractable radioactivity were very low (<0.001 ppm). Instead, characterization of the residues in the grain was conducted by partitioning of the concentrated extracts of the grain with ethyl acetate. In addition to the analyses of the acetone/water extracts, acid or base treatments were used to cleave conjugates to permit the analysis of the exocons released by hydrolysis of those conjugates.				
Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
Corn immature plant (thinnings)	Tioxazafen	Tioxazafen	Thenoyl-benzamidoxime malonylglucoside; Benzamide; Benzamidine	Thenoyl-benzamidoxime malonylglucoside
Corn forage	Benzamidine; Benzoic acid-forming metabolites/ conjugates	2-Thiophenecarboxylic acid forming metabolites/ conjugates	Benzoic Acid*; Benzamide	Tioxazafen; 2-Thiophenecarboxylic Acid*; 2-Thiophene-carboxamide*
Corn stover	Benzamidine; Benzoic acid-forming metabolites/ conjugates	2-Thiophenecarboxylic acid forming metabolites/ conjugates	Benzoic Acid*; Benzamide	2-Thiophenecarboxylic Acid*; 2-Thiophnene-carboxamide*
*Radioactivity in HPLC regions of benzoic acid, 2-thiophenecarboxylic acid and 2-thiophenecarboxamide was not confirmed by TLC.				
Proposed Metabolic Scheme in Corn				



NATURE OF THE RESIDUE IN COTTON	PMRA # 2483579
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen (PH-label) [oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen (TH-label)
Test Site	The treated Pima cotton seeds (*Gossypium barbadense*, PhytoGen PHY 800 PIMA) seeds were planted outdoors in a loamy sand soil in 16 ft^2 plastic-lined wooden boxes.
Treatment	The solid radiolabeled tioxazafen test substances were separately formulated as aqueous suspension concentrates, by wet-milling to a very small particle size, and applied as seed coatings to cotton seed previously coated with fungicide (2-(thiocyanomethylthio) benzothiazole) and insecticide (chlorpyrifos and acephate).
Total Rate	Target: 1.0 mg a.i./seed [0.24 kg a.i./ha*] Actual: PH-label: 1.20 mg a.i./ seed [0.28 kg a.i./ha] TH-label: 1.30 mg a.i./ seed [0.31 kg a.i./ha] *Based on a seeding rate of 35 seeds/plot and 1.0 mg tioxazafen per seed.
Formulation	Aqueous suspension concentrate
Preharvest interval	Immature cotton plants (~5 node growth stage) were harvested as thinnings 39 days after planting (39-DAP); approximately 2 weeks after emergence. Mature undelinted cotton seed, and leaves and stems were harvested 183-DAP.

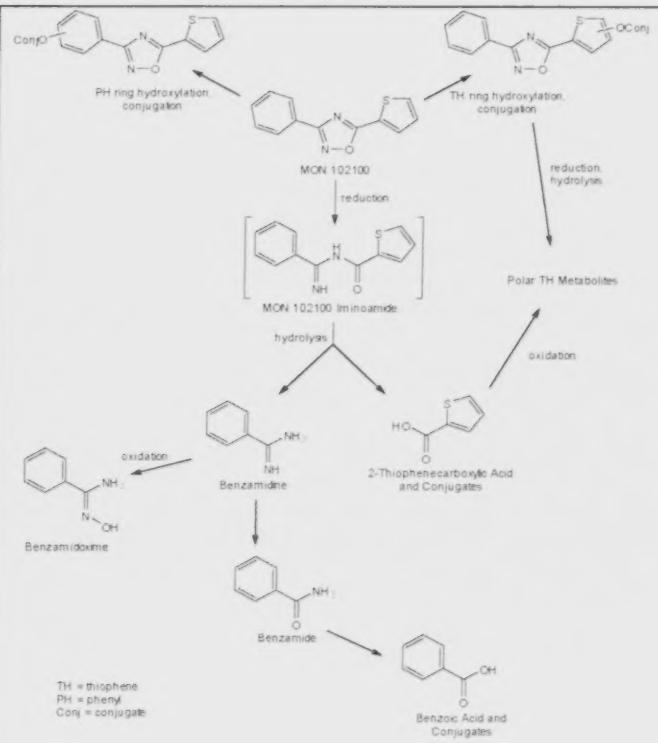
Matrices	PHI (DAP)	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
		TRRs (ppm)	TRRs (ppm)
Cotton immature plants (thinnings)	39	1.0394	2.4031
Cotton mature leaves/stems	183	0.0653	0.0632
Cotton mature undelinted seed	183	0.0087	0.0090

Total radioactive residues (TRRs) were determined by direct combustion and LSC, except for mature undelinted seed (recombined seed and lint) for which the TRRs were determined by summation of the TRRs in the extract and post-extraction solids. ^{14}C-Residues were <0.0001 ppm in all control samples of thinnings, leaves/stems and undelinted seed. The TRRs were expressed as tioxazafen equivalents. Cotton matrices were subjected to exhaustive extraction procedures. Thinnings were initially extracted three times with 80:20 (v/v) acetone:water and then one time with 40:60 acetone:water. Leaves/ stems were extracted four times with 40:60 acetone:water. Undelinted seed (recombined seed and lint) was extracted four times with hexane to remove oils, then once with acetone followed by two extractions with 40:60 acetone:water. The post-extractable solids (PES) from thinnings and leaves/stems extractions were used to investigate the release of unextracted residues through extractions with mild and strong base. Metabolites in the acetone/water extracts of thinnings and leaves/stems were identified primarily by HPLC with reference standards, and their identities were confirmed by TLC. The ^{14}C-residues in the cotton mature undelinted cotton seed extracts of both labels were not analyzed due to low levels of radioactivity (≤0.004 ppm). General characterization of the residues in the undelinted seed was conducted by extraction of the seed with hexane and back-extraction with acetonitrile to characterize residues in the extracted oil fraction, followed by extraction with acetone:water to determine levels of extractable residues in the meal fraction.

Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
Cotton immature plant (thinnings)	None	Tioxazafen	Tioxazafen; Benzoic Acid; Benzamide; Benzamidine	2-Thiophenecarboxylic Acid*; 2-Thiophenecarboxamide*
Cotton mature leaves/stems	MON 102100 Iminoamide**; Benzamidine	None	Benzoic Acid*; Benzamide	2-Thiophenecarboxylic Acid*

*Radioactivity in HPLC regions of benzoic acid, 2-thiophenecarboxylic acid and 2-thiophenecarboxamide was not confirmed by TLC.
**Not confirmed by TLC.

Proposed Metabolic Scheme in Cotton



NATURE OF THE RESIDUE IN SOYBEAN	PMRA # 2483577
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen (PH-label); [oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen (TH-label)
Test Site	The treated soybean seeds (*Glycine max* L., Asgrow® AG4606, a commercial Roundup Ready® STS® soybean variety tolerant to glyphosate and acetolactate synthase inhibitor herbicides) were planted outdoors in a loamy sand soil in 9 ft^2 plastic-lined wooden boxes.
Treatment	The solid radiolabeled tioxazafen test substances were separately formulated as aqueous suspension concentrates, by wet-milling to a very small particle size, and applied as seed coatings to untreated seed together with Acceleron® fungicide/insecticide seed treatment formulation. The Acceleron® formulation was prepared using a seed colorant, finishing polymer, insecticide (imidacloprid) and fungicide (metalaxyl and pyraclostrobin).
Total Rate	Target: 1.0 mg a.i./seed [0.62 kg a.i./ha*] Actual: PH-label: 1.20 mg a.i./ seed [0.28 kg a.i./ha] TH-label: 1.30 mg a.i./ seed [0.31 kg a.i./ha] *Based on a seeding rate of 52 seeds/plot and 1.0 mg tioxazafen per seed.
Formulation	Aqueous suspension concentrate
Preharvest interval	Immature plant samples at the 1st trifoliate unfolded stage (BBCH 12 growth stage, approximately V1) were collected as thinnings 28 days after planting (28-DAP); forage samples were collected 48-DAP at the BBCH 17 growth stage (approximately V7); hay samples were cut 82-DAP when plants were mid- to

	full-bloom, or when pods were about 50% developed, and dried in the field for 6 days (86-DAP) to a moisture content of about 10-20% ; and samples of mature seed were collected 147-DAP.		
Matrices	PHI (DAP)	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
		TRRs (ppm)	TRRs (ppm)
Soybean immature plants (thinnings)	28	9.05	10.9
Soybean forage	48	0.426	0.510
Soybean hay	82	0.779	1.06
Soybean seed	147	0.0696	0.165

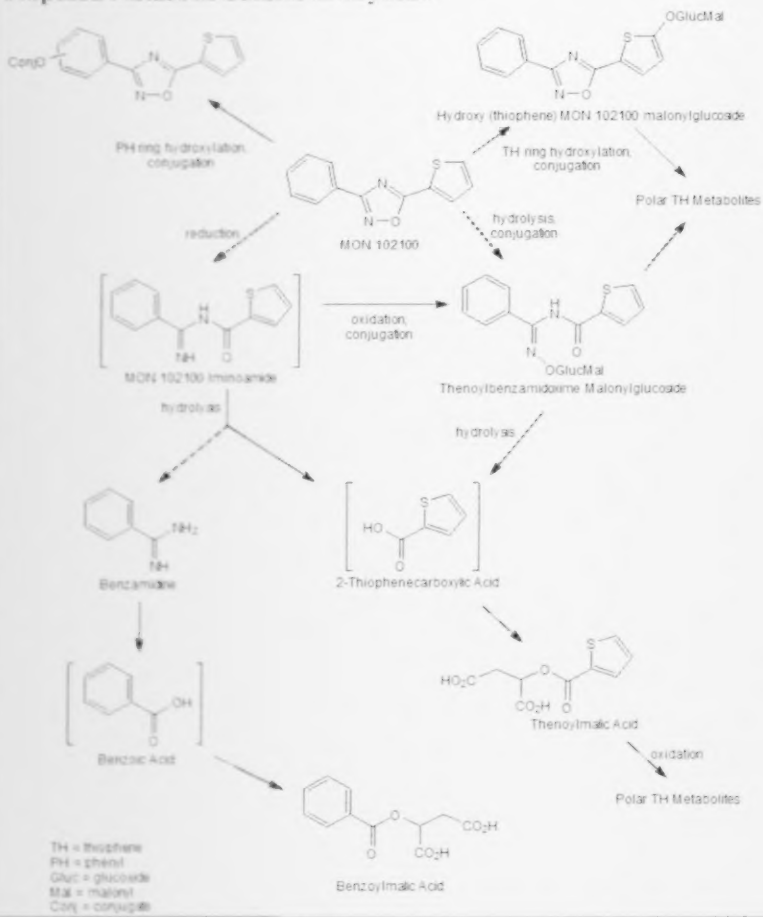
Total radioactive residues (TRRs) were determined by direct combustion and LSC, and expressed as tioxazafen equivalents. ^{14}C-Residues were <0.0001 ppm in all control samples of soybean thinnings, forage, hay and seed. Soybean matrices were subjected to exhaustive extraction procedures. Thinnings were extracted using the following procedure: three times with 80:20 (v/v) acetone:water, once time with 40:60 acetone:water, and twice times with 20:80 acetone:water. Forage and hay samples were extracted four times with 40:60 acetone:water. Seed samples were extracted three times with hexanes to remove oils, then once with acetone followed by four extractions with 40:60 acetone:water. The PES from the initial forage and hay extractions was used to investigate the release of unextracted residues through extractions with acid and base, and a series of chemical and enzymatic digestions. Metabolites in thinnings, forage and hay were identified by HPLC with reference standards, and by gas chromatography mass spectrometry (GC-MS) and liquid chromatography mass spectrometry (LC-MS). ^{14}C-Residues in the hexane soybean seed extract were not analyzed due to low levels of radioactivity. However, partitioning with acetonitrile indicated that very little of the ^{14}C-residues in soybean seed in the oil fraction (0.0006-0.0008 ppm) was due to tioxazafen or molecules of similar polarity.

Metabolites Identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
Soybean thinnings	Benzamidine	None	Tioxazafen; Benzoylmalic Acid; Thenoylbenza-midoxime malonylglucoside; Hydroxy (thiophene) MON 102100 malonylglucoside	Tioxazafen; Thenoylmalic Acid; Thenoylbenza-midoxime malonylglucoside; Hydroxy (thiophene) MON 102100 malonylglucoside
Soybean forage	Tioxazafen	None	Benzamidine; Thenoylbenza-midoxime malonylglucoside; Hydroxy (thiophene) MON 102100 malonylglucoside	Tioxazafen; Thenoylbenza-midoxime malonylglucoside; Hydroxy (thiophene) MON 102100 malonylglucoside

Soybean hay	None	None	Tioxazafen; Benzamidine; Thenoylbenza-midoxime malonylglucoside; Hydroxy (thiophene) MON 102100 malonylglucoside	Tioxazafen; Thenoylbenza-midoxime malonylglucoside; Hydroxy (thiophene) MON 102100 malonylglucoside
Soybean seed	Benzamidine	None	Tioxazafen*; Hydroxy (thiophene) MON 102100 malonylglucoside	Tioxazafen*

*Tioxazafen was not actually identified in the hexane extracts, rather the levels were based on the percentage of radioactivity extracted into acetonitrile from the hexane extracts.

Proposed Metabolic Scheme in Soybean



CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, radish and wheat		PMRA # 2483199
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen (PH-label); [oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen (TH-label)	
Test site	The field phase of the study was conducted in outdoor fenced-off research plots near Madera, CA (NAFTA Growing Region 10). Twelve plots (boxes) were established: four control plots, four PH-T-treated plots, and four TH-T-treated plots. All twelve plots (1.0 m^2) contained sandy loam soil. The interior of each wooden box was lined with a heavy gauge plastic liner.	
Formulation	Aqueous suspension concentrate.	
Application rate and timing	The solid radiolabeled tioxazafen test substances were separately formulated as aqueous suspension concentrates, by wet-milling to a very small particle size, and applied as seed coatings to untreated corn seed together with Acceleron® fungicide/insecticide seed treatment formulation. The Acceleron® formulation was prepared using a seed colorant, finishing polymer, insecticide (clothianidin) and fungicide (metalaxyl, trifloxystrobin and ipconazole). Based on the soil surface area of each plot of 1.0 m^2, for an application rate of 0.32 kg a.i. /ha, the minimum amount of each test substance required per box was 32 mg, which was achieved by planting of 64 seeds (treated at a target rate of 0.5 mg a.i./seed) per plot. In order to achieve a uniform application across the plot, the seeds were planted in an 8 × 8 grid pattern, with 11 cm spacing between seeds. The achieved application rates were 0.30 kg a.i./ha (0.47 mg a.i./seed; PH-label) and 0.35 kg a.i./ha (0.55 mg a.i./seed; TH-label). The primary corn crop in all test plots was cut off near the soil surface 21 days after planting (~2 weeks after emergence), and the plants were roughly chopped and tilled into the soil. The rotational crops lettuce, radish and wheat were planted at various plant-back intervals (PBIs): 30 days, 120 days, 360 days (except lettuce) and 413 days (lettuce). All crop commodities were successfully harvested from the plots, except 360-day PBI lettuce, which due to crop failure was replanted at 413 days. For each PBI, radish and lettuce were planted in the same box separated by a divider; wheat was planted in a separate box. The 30- and 360-day PBIs were made in the same boxes. Samples of each rotational crop commodity were harvested 48-89 days after planting (DAP) for immature lettuce, 81-110 DAP for mature lettuce, 73-82 DAP for radish , 29-46 DAP for wheat forage, and 138-232 days for wheat grain and straw. Wheat hay was cut 95-139 DAP, and was dried in the fields for 4-24 days prior to collection.	
Total radioactive residues (TRRs) were determined by direct combustion and liquid scintillation counting (LSC), and expressed as tioxazafen equivalents. Samples were extracted with acetone/water (40:60, v/v; 2-4x), and the extracts were analyzed by HPLC with reference standards. A number of experiments were conducted on both the PH-T and TH-T 30-d PBI wheat forage extract concentrates in order to characterize the residues. The following samples were not extracted due to low ^{14}C-residues: 413-day PBI immature and mature lettuce (both labels), 360-day PBI radish top samples (both labels), 360-day PBI radish root (PH-T) and 360-day PBI wheat grain (both labels). The 120-day PBI wheat grain extracts for both labels were not analyzed due to low ^{14}C-residues levels.		
Metabolites Identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)

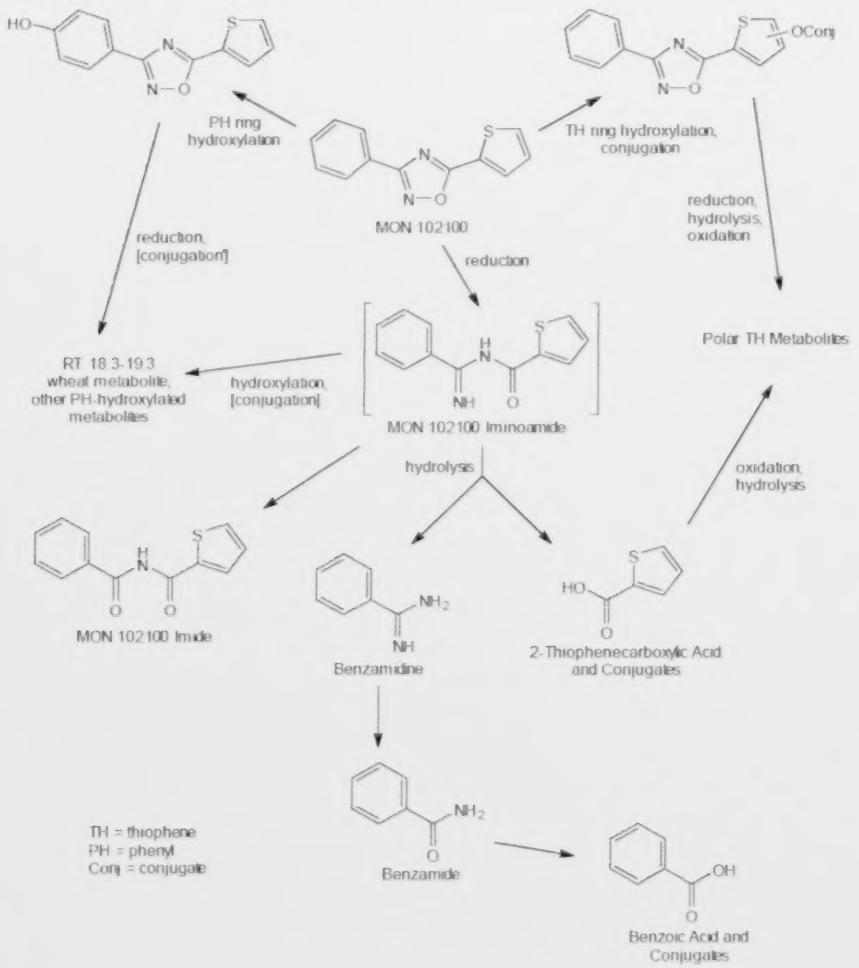
Matrices	PBI (days)	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
Lettuce (immature)	30	None	None	Benzamidine; Benzoic Acid*	Tioxazafen
	120	None	None	Tioxazafen; MON 102100 Imide; Benzamidine	2-Thiophenecarboxamide
	413	Samples not extracted; TRRs = 0.0038 ppm (PH-label) and 0.0025 ppm (TH-label).			
Lettuce (mature)	30	None	None	Benzamidine	Tioxazafen
	120	None	None	Tioxazafen; MON 102100 Imide; Benzamidine; Benzoic Acid*	Tioxazafen; 2-Thiophenecarboxylic Acid*; 2-Thiophene-carboxamide
	413	Samples not extracted; TRRs = 0.0023 ppm (PH-label) and 0.0030 ppm (TH-label).			
Radish Tops	30	None	2-Thiophene carboxylic Acid**	MON 102100 Imide; Benzoic Acid; MON 102100 Iminoamide; Benzamide*; Benzamidine	MON 102100 Imide*; 2-Thiophene carboxamide*
	120	None	2-Thiophene carboxylic Acid**	Tioxazafen; MON 102100 Imide; Benzoic acid; MON 102100 Iminoamide; Benzamide*; Benzamidine	MON 102100 Imide*; 2-Thiophene carboxamide*
	360	Samples not extracted; TRRs = 0.0014 ppm (PH-label) and 0.0050 ppm (TH-label).			
Radish Roots	30	None	None	Benzoic acid***; MON 102100 Iminoamide; Benzamidine	2-Thiophene carboxylic Acid*; 2-Thiophene-carboxamide
	120	Benzoic Acid***	2-Thiophene carboxylic Acid*	MON 102100 Imide; MON 102100 Iminoamide; Benzamidine	MON 102100 Imide*; MON 102100 Iminoamide*

	360	Sample not extracted; TRR = 0.0054 ppm	None	Sample not extracted; TRR = 0.0054 ppm	2-Thiophene carboxylic Acid*
Wheat Forage	30	None	2-Thiophene carboxylic Acid****	MON 102100 Imide; Benzoic Acid*; Benzamide; Benzamidine	MON 102100 Imide; MON 102100 Iminoamide; 2-Thiophene carboxamide
	120	None	2-Thiophene carboxylic Acid****	Tioxazafen; MON 102100 Imide; Benzoic Acid*; MON 102100 Iminoamide; Benzamide; Benzamidine	MON 102100 Imide; MON 102100 Iminoamide
	360	None	None	Benzoic Acid*; Benzamidine	2-Thiophene carboxylic Acid****
Wheat Hay	30	None	None	Benzoic Acid*; MON 102100 Iminoamide; Benzamidine	MON 102100 Imide; 2-Thiophene carboxylic Acid*
	120	None	None	Tioxazafen; MON 102100 Imide; Benzoic Acid*; Benzamidine	MON 102100 Imide; 2-Thiophene carboxylic Acid*
	360	None	None	Benzoic Acid*; Benzamidine	2-Thiophene carboxylic Acid*
Wheat Straw	30	None	None	Tioxazafen; MON 102100 Imide; Benzamidine	Tioxazafen; MON 102100 Imide; 2-Thiophene carboxylic Acid*****
	120	None	None	Tioxazafen; MON 102100 Imide; Benzoic Acid*; MON 102100 Iminoamide; Benzamidine	Tioxazafen; 2-Thiophene-carboxylic Acid*****; 2-Thiophene carboxamide
	360	None	None	MON 102100 Imide; MON 102100 Iminoamide	None
Wheat Grain	30	None	None	Benzamidine	None
	120	Samples (TRR = 0.0070 ppm PH-label and 0.0050 ppm TH-label) were extracted, but were not analyzed.			

	360	Samples were not extracted (TRR = 0.0029 ppm PH-label and 0.0032 ppm TH-label).

*Tentatively identified.
** Although there was a peak with a retention time consistent with that of 2-thiophenecarboxylic acid, the peak was also present in the 120-day PH-T radish foliage extract. Therefore, the peak is likely predominantly a metabolite other than 2-thiophenecarboxylic acid.
*** Although there was a peak with a retention time corresponding to that of benzoic acid in the PH-T radish root extract for the 30- and 120-day PBIs, the peak was also present in the TH-T radish root extract profiles.
****Similar peaks were observed in PH-T wheat forage; therefore, this peak is predominantly not 2-thiophenecarboxylic acid.
***** A peak consistent with 2-thiophenecarboxylic acid was detected, but it was also present in 30-day PHT-wheat straw. Therefore, it is unlikely to be 2-thiophenecarboxylic acid

Proposed Metabolic Scheme in Rotational Lettuce, Radish and Wheat



Note:
A metabolite eluting in the region of 18.3-19.3 min. in both the PH-T and TH-T rotational crop samples was found at >10% TRR in some matrices, especially wheat foliage, but the absolute amount was <0.01 ppm in all samples analyzed. The hydrolysis experiments conducted on 30-day PBI wheat forage (PH-T and TH-T) suggest that the RT 18.3-19.3 min. unknown metabolite in wheat has limited stability, is hydroxylated at the 4-position of the phenyl ring, contains an acidic moiety (i.e., carboxylic acid) possibly through conjugation or oxidative opening of the thiophene ring, the oxadiazole ring is opened, and the metabolite may be a conjugate.

NATURE OF THE RESIDUE IN LAYING HEN	PMRA # 2493775

The metabolism of tioxazafen was examined in laying hens using either [oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen (PH-label) or [oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen (TH-label). Hens (10 per treatment group) were dosed daily via gelatin capsule with tioxazafen for a period of seven days at doses corresponding to 10.5 ppm (PH-label) and 10.8 ppm (TH-label) as fed. There was no control hen. Eggs and excreta were collected twice daily. Hens were sacrificed 19-21.5 hours after the last dose was administered. The liver, breast and thigh muscle, abdominal and subcutaneous fat, and gastrointestinal tract with contents were collected at sacrifice. Total radioactive residues (TRRs) were determined by direct combustion and LSC for excreta and homogenized GI tracts. The TRR in liver, muscle, eggs and fat was measured by solubilization of subsamples with tissue solubilizer. Radioactivity in cage washes was determined directly by LSC. Liver, muscle, egg and excreta samples were each extracted with aqueous acetonitrile (2x) and acetonitrile (1x) to solubilize radioactive residues. Fat was extracted with hexane/acetone (1x) and then with acetone (2x), and the combined hexane/acetone extract was partitioned with acetonitrile. Radioactive residues in tissue and excreta aqueous acetonitrile extracts were analyzed by HPLC. Egg acetonitrile-soluble fractions were analyzed by HPLC, and the hexane phase from partitioning was analyzed by TLC. Metabolites were identified primarily by co-chromatography with reference standards, and their identities were confirmed by TLC. Gas chromatography/mass spectrometry (GC/MS) was also utilized for metabolite identification. Excreta extracts contained multiple residues that were poorly resolved by HPLC.

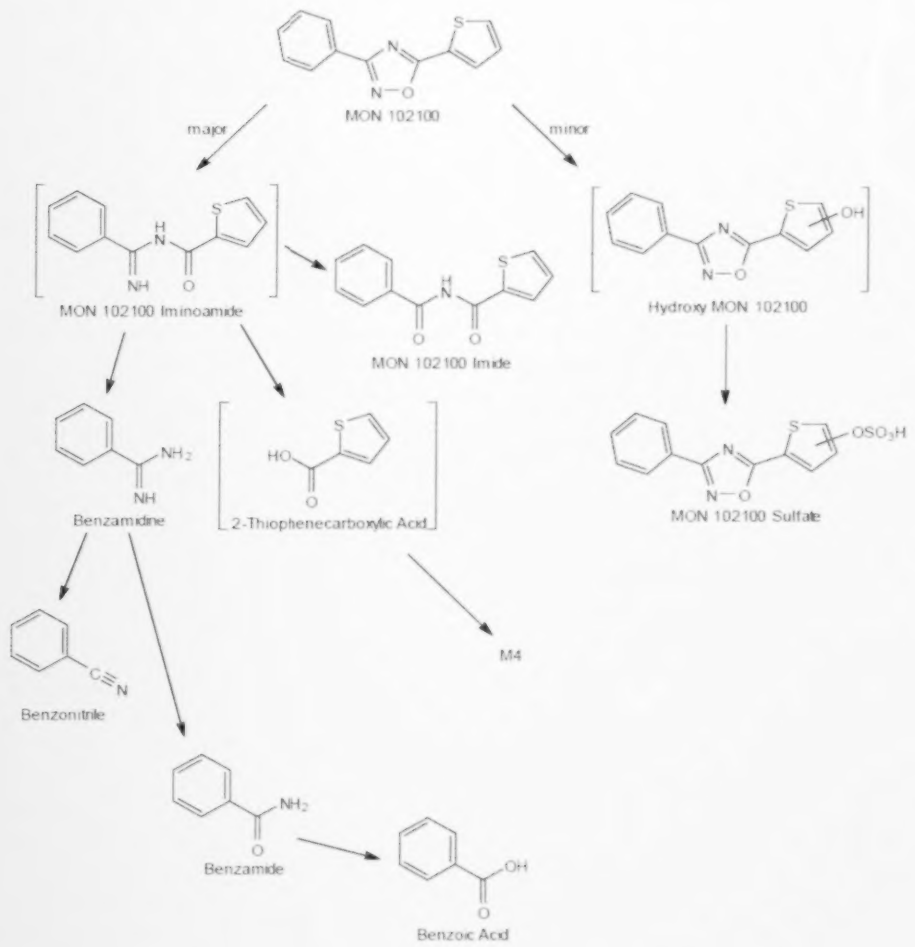
Matrices	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen		[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	
	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Excreta				
Excreta	Not reported	88.5	Not reported	87.7
Gastrointestinal Tract (GI) Plus Contents	Not reported	1.1	Not reported	1.5
Cage Wash	Not reported	0.4	Not reported	0.5
Tissues and Eggs				
Thigh Muscle	0.014	0.01	0.015	0.01
Breast Muscle	0.009	0.01	0.009	0.01
Abdominal Fat	0.045	0.02	0.046	0.01
Subcutaneous Fat	0.044	0.01	0.039	0.01
Liver	0.612	0.32	0.664	0.33
Eggs*	--	0.33	--	0.36
Total Recovery	90.7%		90.4%	

*Cumulative percent of dose for entire egg collection; ^{14}C-residues in eggs from solubilization ranged from ND (not detected) to 0.149 ppm for the PH-label and from ND to 0.177 ppm for the TH-label.

Metabolites identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
Abdominal Fat	Tioxazafen; Benzonitrile	Tioxazafen	None	None
Subcutaneous Fat	Tioxazafen; Benzonitrile	Tioxazafen	None	None
Breast Muscle	Benzamidine	M4*	Tioxazafen; M1**	M1**
Thigh Muscle	Benzamidine	M4*	Tioxazafen; M1**	Tioxazafen; M1**
Liver	Benzoic acid	None	Tioxazafen; MON 102100 Imide; M1**; Benzamide; Benzamidine	Tioxazafen; MON 102100 Imide; M1**; M4*
Egg (Day 5 AM)	None	None	Tioxazafen; MON 102100 Imide; M1**; Hydroxy MON 102100 Sulfate; Benzamidine	Tioxazafen; MON 102100 Imide; M1**; Hydroxy MON 102100 Sulfate
Egg (Day 8 AM)	None	None	Tioxazafen; MON 102100 Imide; M1**; Hydroxy MON 102100 Sulfate; Benzamide; Benzamidine	Tioxazafen; MON 102100 Imide; M1**; Hydroxy MON 102100 Sulfate; M4*

* M4: A thiophene-specific very polar residue, which is possibly a mixture of metabolites.
** M1: Functionalized MON 102100 structure, possibly hydroxylated and conjugated to glucuronic acid.

Proposed Metabolic Scheme in the Hen



NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA # 2483529

The metabolism of tioxazafen was examined in lactating goats using either [oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen (PH-label) or [oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen (TH-label). Goats (one animal per treatment group) were dosed daily via gelatin capsule with tioxazafen for a period of five days at a dose corresponding to 10.6 ppm as fed. There was no control goat.

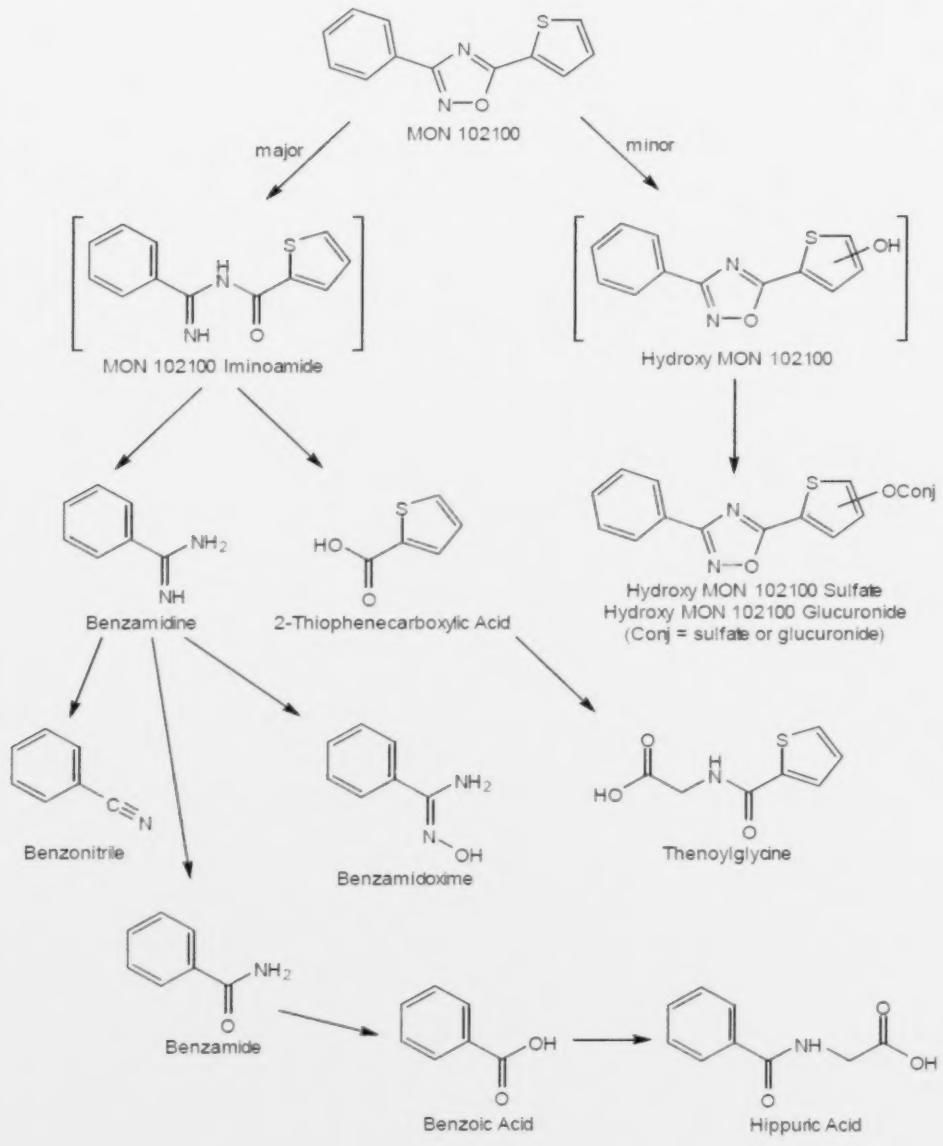
Milk, urine and feces were collected twice daily, in the morning before dosing and in the evening. The goats were sacrificed 18-19 hr after administration of the last dose. The following tissues were removed for analysis: liver, kidney, flank and loin muscle, omental, subcutaneous and renal fat, gastrointestinal (GI) tract with contents, bile and blood. Total radioactive residues (TRRs) were determined by direct combustion and LSC for feces, GI tract, and blood, by direct LSC analysis for bile, urine, cage washes and skim milk, and by solubilization and LSC analysis for tissues and milk fat. For a given sample, the TRR in whole milk was calculated as follows: TRR = [µg (skim milk) + µg (milk fat)] ÷ [Total Mass].

Liver, kidney, muscle (flank and loin) and feces were each extracted twice with acetonitrile/water (1:1, v/v; 2x) followed by extraction with acetonitrile (1x) to solubilize radioactive residues. Milk was separated into skim milk and milk fat by centrifugation, and skim milk was extracted with acetone (1x) and acetone/water (1:1, v/v; 2x) followed by a final acetone extraction. Milk fat, omental fat, renal fat and subcutaneous fat were each extracted with hexane/acetone (4:1, 1x) followed by acetone (2x); the hexane/acetone extracts were concentrated and partitioned between hexane and ACN (3x). All TH-label samples of fat and muscle were not subjected to extraction as the TRR in each was <0.001 ppm.

Matrices	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen		[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	
	TRRs (ppm)	% of Administered Dose	TRRs (ppm)	% of Administered Dose
Excreta				
Feces	Not reported	64.50	Not reported	33.43
Gastrointestinal (GI) Tract Plus Contents	Not reported	5.41	Not reported	2.86
Urine	Not reported	19.93	Not reported	49.55
Cage Wash	Not reported	0.35	Not reported	0.25
Tissues and Milk				
Flank Muscle	0.052	0.01	<0.001*	Not reported
Loin Muscle	0.055	0.03	<0.001*	Not reported
Omental Fat	0.015	0.01	<0.001*	Not reported
Subcutaneous Fat	0.018	<0.01	<0.001*	Not reported
Renal Fat	0.014	<0.01	<0.001*	Not reported
Kidney	0.383	0.04	0.217	0.03
Liver	1.095	0.53	0.334	0.29
Skim Milk**	0.026	0.05	0.083	0.18
Milk Fat**	0.256	0.03	0.268	0.06
Blood	0.049	<0.01	0.039	<0.01
Bile	0.371	<0.01	0.194	<0.01
Total Recovery	90.9		86.7	

* Samples of fat and muscle were not subjected to extraction and subsequent analysis as the TRR were <0.001 ppm. ** Cumulative percent of dose for entire milk collection; ppm values for Day 2 milk only.				
Metabolites identified	Major Metabolites (>10% of the TRRs)		Minor Metabolites (<10% of the TRRs)	
Radiolabel Position	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen	[oxadiazole-3-^{13}C, phenyl-UL-^{14}C]-tioxazafen	[oxadiazole-5-^{13}C, thiophene-2-^{14}C]-tioxazafen
Liver	Benzoic Acid; Benzamidine	None	Benzamide	2-Thiophenecarboxylic Acid; Thenoylglycine
Kidney	Benzamide; Benzamidine	Thenoylglycine	Benzoic Acid	2-Thiophenecarboxylic Acid
Omental Fat	Benzamidine	Not Extracted/ Analyzed	Tioxazafen; Benzonitrile	Not Extracted/ Analyzed
Subcutaneous Fat	Tioxazafen; Benzamidine	Not Extracted/ Analyzed	Benzonitrile	Not Extracted/ Analyzed
Renal Fat	Benzamidine	Not Extracted/ Analyzed	Benzonitrile	Not Extracted/ Analyzed
Flank Muscle	Benzamidine	Not Extracted/ Analyzed	None	Not Extracted/ Analyzed
Loin Muscle	Benzamidine	Not Extracted/ Analyzed	None	Not Extracted/ Analyzed
Skim Milk (Day 2 PM)	Hydroxy MON 102100 Glucuronide; Benzamidine	Thenoylglycine	Benzoic Acid; Benzamide	Hydroxy MON 102100 Glucuronide
Milk Fat (Day 2 PM)	Hydroxy MON 102100 Sulfate	Thenoylglycine; Hydroxy MON 102100 Sulfate	Hydroxy MON 102100 Glucuronide	Hydroxy MON 102100 Glucuronide
Whole Milk* (Day 2 PM)	Hydroxy MON 102100 Glucuronide; Hydroxy MON 102100 Sulfate; Benzamidine	Thenoylglycine; Hydroxy MON 102100 Sulfate	Benzoic Acid; Benzamide	Hydroxy MON 102100 Glucuronide
Feces (Composite Days 1-6)	Benzamidine	2-Thiophenecarboxylic Acid	Benzoic Acid; Benzamide	None
Urine (Composite Days 1-6)	Benzamidine	Thenoylglycine	Benzoic Acid; Benzamide; Hippuric Acid**; Benzamidoxime	2-Thiophenecarboxylic Acid
*Calculated by the study author based on the residues in skim milk and milk fat. **The glycine conjugate of benzoic acid.				

Proposed Metabolic Scheme in the Goat



FREEZER STORAGE STABILITY	PMRA # 2483116, 2553809
Plant matrices: Corn (grain), lettuce (leaves), radish (root), orange (whole), soybean (seed) and lentil (seed). The freezer storage stability data indicate that residues of tioxazafen and the metabolite benzamidine are stable at ~-20°C for at least 9 months in all plant matrices including processed fractions. Animal matrices: Cattle milk, kidney and fat; poultry liver, muscle and eggs. The stability of tioxazafen and the metabolite benzamidine was evaluated in all selected matrices. In addition, the stability of the metabolite 2-thenoylglycine was evaluated in milk, liver and kidney, and the stability of the metabolite benzonitrile was evaluated in fat. Storage conditions and duration were chosen to represent those utilized for storage of residue samples during the poultry (PMRA No. 2483141) and cattle (PMRA No. 2483123) feeding studies. The freezer storage stability data indicate that residues of tioxazafen and the metabolite benzamidine are stable at -18°C for at least 7 months in milk, liver, kidney and muscle, and for at least 6 months in fat and eggs; residues of the metabolite thenoylglycine are stable at -18°C in milk, liver and kidney for at least 7 months; and residues of metabolite benzonitrile are stable at -18°C in fat for at least 6 months.	
CROP FIELD TRIALS & RESIDUE DECLINE ON COTTON	PMRA # 2483119
Field trials were conducted in 2013 in the United States in NAFTA Growing Regions 2 (SC and GA; 2 trials), 4 (MS, MO, LA; 3 trials), 6 (TX; 2 trials), 8 (TX and OK; 4 trials), and 10 (CA; 1 trial) for a total of twelve trials. The above trial count reflects one pair of trials determined to be replicate trials. Each trial consisted of one untreated plot and two side-by-side treated plots reflecting seed treatment with a 540 g a.i./L suspension concentrate (SC) formulation of tioxazafen (MON 102119, containing 47.3-47.8% a.i.) at 0.96 or 2.07 mg tioxazafen/seed, respectively (1254 g a.i./100 kg seed and 2704 g a.i./100 kg seed, respectively). Seed was treated using a lab-scale Gustafson Batch Modular Coater. All treatments included Acceleron® (insecticide/fungicide), colourant and polymer seed finisher. Talc and $CaCO_3$ were also added to the slurry to help the seed dry and prevent sticking. Treated seed was planted within 94 days of treatment at planting densities of 43,560-72,397 seed/A. Field application rates of 0.103-0.171 and 0.223-0.370 kg a.i./ha were calculated from actual seed treatment rates and planting densities. Samples of cotton seed were harvested 146-183 days after planting (DAP) by hand and/or picker and stripper equipment. Samples were ginned at field sites within 26 hours of harvest to produce samples of undelinted cotton seed from all trials and cotton gin byproducts from the four trials in OK and TX that were harvested using stripper equipment. Decline samples of undelinted seed and gin byproducts were collected from trials 08TX and 09TX (high rate plots only) 7 days before and 7 and 14 days after target harvest: 146/163, 159/177, and 166/184 DAP. In the residue decline trials, residues of the metabolite benzamidine in/on cotton gin byproducts generally declined after the target harvest. Residues of tioxazafen were below the LOQ in/on all samples of cotton gin byproducts from both trials; therefore, residue decline could not be assessed. Residues of both tioxazafen and the metabolite benzamidine were below the LOQ in/on all samples of undelinted cotton seed from both trials; therefore, residue decline could not be assessed.	

Commodity	Nominal Application rate (mg a.i./seed)	DAP (days)	Residue Levels (ppm Tioxazafen Equivalents)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Combined Residues (Tioxazafen + Benzamidine)										
Cotton Undelinted Seed	1	146-183	12	<0.0050	<0.0050	<0.0050	<0.0050	0.005	0.005	NA
	2	146-183	12	<0.0050	<0.0050	<0.0050	<0.0050	0.005	0.005	NA
Cotton Gin Byproducts	1	151-183	4	<0.0050	<0.0125	<0.0052	<0.0098	0.0064	0.0069	0.0020
	2	151-183	4	<0.0050	<0.0242	<0.0055	<0.0153	0.0102	0.0103	0.0042

LOQ = 0.0025 per analyte in each cotton matrix.
Residues of tioxazafen were <LOQ in/on all samples of cotton gin byproducts.
Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON FIELD CORN	PMRA # 2483117

Field trials were conducted in 2012 in the United States in NAFTA Growing Regions 1 (PA; 1 trial), 2 (NC; 1 trial), 5 (MI, IN, IL, IA, MO, NE, MN, and WI; 15 trials), and 6 (TX and OK; 2 trials) for a total of nineteen trials. The above trial count reflects three pairs of trials determined to be replicate trials.

Each trial consisted of one untreated plot and three side-by-side treated plots reflecting seed treatment with a 540 g a.i./L suspension concentrate (SC) formulation of tioxazafen (MON 102116, containing 48.7.8% a.i.) at 0.513-0.543, 1.022-1.065, or 2.051-2.263 mg tioxazafen/seed (162-211, 326-411 and 662-848 g a.i./100 kg seed, respectively). Seed was treated using a lab-scale Gustafson Batch Modular Coater. All treatments included Acceleron® insecticide/fungicide, colorant and polymer seed finisher. Treated seed was planted within 99 days of treatment at planting densities of 24,248-35,545 seed/A. Field application rates of 0.031-0.046, 0.068-0.093, and 0.132-0.189 kg a.i./ha were calculated from actual seed treatment rates and seed planting densities. Samples of forage were harvested 86-117 days after planting (DAP) and samples of grain and stover were harvested 113-165 DAP. Decline samples were collected from trials 09IA and 15NE (high rate plots only) 7 days before target harvest (all matrices) and 7 and 14 days (forage) or 14 and 28 days (grain and stover) after target harvest: 104/95, 118/109, 125/116 DAP for forage and 139/145, 160/166, and 174/180 DAP for grain and stover.

In the residue decline trials, residues declined in forage based on tioxazafen residues very near the LOQ in samples from the first harvest interval only at the 09IA trial. Residues of both analytes were below the LOQ in/on all remaining samples from both trials; therefore, residue decline could not be assessed.

Commodity	Nominal Application rate (mg a.i./seed)	DAP (days)	Residue Levels (ppm Tioxazafen Equivalents)							
			n	Min. [a]	Max. [a]	LAFT [b]	HAFT [b]	Median [b]	Mean [b]	SD [b]
Combined Residues (Tioxazafen + Benzamidine)										
Field Corn Forage	0.5	86-117	19	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.005	NA
	1		19	<0.0050	<0.0083	<0.0050	<0.0081	0.0050	0.0052	0.0007
	2		19	<0.0050	<0.0114	<0.0050	<0.0105	0.0050	0.0053	0.0013
Field Corn Grain	0.5	113-165	19	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.005	NA
	1		19	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.005	NA
	2		19	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.005	NA
Field Corn Stover	0.5	115-165	19	<0.0050	<0.0204	<0.0050	<0.0148	0.0050	0.0057	0.0022
	1		19	<0.0050	0.0144	<0.0050	<0.0130	0.0050	0.0062	0.0021
	2		19	<0.0050	<0.0217	<0.0050	<0.0135	0.0050	0.0067	0.0027

LOQ = 0.0025 per analyte in each field corn matrix.
[a] Values based on total number of samples.
[b] Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON SOYBEAN	PMRA # 2483118

Field trials were conducted in 2013 in the United States in NAFTA Growing Regions Zones 2 (NC and SC; 2 trials), 4 (AR, MO, MS, LA; 4 trials), and 5 (MI, IN, IL, IA, MO, NE, MN, and WI; 14 trials) for a total of twenty trials. The above trial count reflects two pairs of trials determined to be replicate trials.

Each trial consisted of one untreated plot and two side-by-side treated plots reflecting seed treatment with a 540 g a.i./L suspension concentrate (SC) formulation of tioxazafen (MON 102119, containing 47.3% a.i.) at 0.457-0.568 or 0.880-1.09 mg tioxazafen/seed (274-413 g a.i./100 kg seed and 527-674 g a.i./100 kg seed, respectively). Seed was treated using a lab-scale Gustafson Batch Modular Coater. All treatments included Acceleron® insecticide/fungicide, colorant and polymer seed finisher. Treated seed was planted within 101 days of treatment at planting densities of 88,348-209,836 seed/A. Field application rates of 0.148-0.258 and 0.192-0.473 kg a.i./ha were calculated from actual seed treatment rates and seed planting densities. Samples of soybean forage, hay, and seed were harvested 39-78, 46-86, and 111-176 days after planting (DAP), respectively. Hay samples were allowed to dry in the field for up to 10 days. Decline samples were collected from trials 12IA and 17NE (high rate plots only) 7 days before and 7 and 14 days after target harvest for forage and hay, and 7, 14, and 21 days after target harvest for seed: 49, 62/64, and 70 DAP for forage; 56, 70, and 76/77 DAP for hay; and 129/148, 136/155, and 143/162 DAP for seed.

In the decline trials, residues of tioxazafen and the metabolite benzamidine generally declined with increasing harvest interval in forage and hay. In seed, residues of tioxazafen were below the LOQ in/on all samples, and residues of the metabolite benzamidine generally remained stable across all harvest intervals.

Commodity	Nominal Application Rate (mg a.i./seed)	DAP (days)	Residue Levels (ppm Tioxazafen Equivalents)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Combined Residues (Tioxazafen + Benzamidine)										
Soybean Forage	0.5	39-78	20	0.0077	0.1123	0.0088	0.0780	0.0323	0.0335	0.0205
	1		20	<0.0090	0.0965	<0.0095	0.0904	0.0418	0.0377	0.0215
Soybean Hay	0.5	46-86	20	0.0240	0.2393	0.0263	0.1687	0.0735	0.0753	0.0365
	1		20	0.0254	0.2026	0.0316	0.1977	0.0891	0.0941	0.0450
Soybean Seed	0.5	111-176	20	<0.0050	<0.0351	<0.0059	<0.0306	0.0127	0.0136	0.0061
	1		20	<0.0072	<0.0476	<0.0080	<0.0474	0.0193	0.0205	0.0096

LOQ = 0.0025 per analyte in each soybean matrix.
# Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of independent field trials.

RESIDUE DATA IN ROTATIONAL CROPS	PMRA # 2483183

Two trials (two each for radish, lettuce, wheat and sorghum) were conducted during the 2013 growing season in NAFTA Growing Regions 2 (NC) and 10 (CA).

Each trial consisted of three untreated plots and three treated plots for each of the three target plant-back intervals (PBIs) of 30-, 120-, and 365-days, reflecting seed treatment with a 573 g a.i./L suspension concentrate (SC) formulation of tioxazafen (MON 102119, containing 47.3% a.i.) on a primary crop (soybean) at 0.568 mg tioxazafen/seed. Seed was treated using a Batch Modular Coater. All treatments included Acceleron® insecticide/fungicide. Treated seed was planted at planting densities of 191,090-247,940 seed/A. Field application rates of 0.293- 0.348 kg a.i./ha were calculated from actual seed treatment rates and seed planting densities. The soil type at the sites was loamy sand. The primary crop (soybean) was removed by either rototilling, mowing, hand cutting, disking or mowing and disking. Rotational crops of lettuce and radish were planted at PBIs of 29-30, 117-124, and 364 days. Rotational crops of sorghum were planted at PBIs of 29-30 and 365 days and rotational crops of wheat were planted at the 124-day PBI. Samples of lettuce leaves were harvested 52-117 days after planting (DAP) and samples of radish (tops and root) were harvested 35-106 DAP. Samples of sorghum forage, grain, and stover were harvested 78-118, 103-151, and 107-151 DAP, respectively. Samples of wheat forage, hay, and grain and straw were harvested 133-202, 161-224, and 202-249 DAP, respectively. Sorghum stover and wheat hay samples were allowed to dry in the field for 0-4 and 5-7 days, respectively, after harvest.

Because quantifiable residues were not observed in the 117- to 124-day PBI rotational crop samples, the 364/365-day samples were not analyzed.

Commodity	Total Application Rate (g a.i./ha)	PBI (days)	Residue Levels (ppm Tioxazafen Equivalents)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Combined Residues (Tioxazafen + Benzamidine)										
Lettuce, leaves	0.293-0.327	29-30	2	<0.0050	<0.0085	<0.0050	<0.0068[1]	0.0059	0.0059	NA
	0.293-0.348	117-124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Radish, tops	0.293-0.327	29-30	2	<0.0050	<0.0067	<0.0053	<0.0063[2]	0.0058	0.0058	NA
	0.293-0.348	117-124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Radish, root	0.293-0.327	29-30	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
	0.293-0.348	117-124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Sorghum, forage	0.293-0.348	29-30	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Sorghum, grain	0.293-0.348	29-30	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Sorghum, stover	0.293-0.348	29-30	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Wheat, forage	0.293-0.348	124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Wheat, hay	0.293-0.348	124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA
Wheat, grain	0.293-0.348	124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA

Wheat, straw	0.293-0.348	124	2	<0.0050	<0.0050	<0.0050	<0.0050	0.0050	0.0050	NA

LOQ = 0.0025 ppm per analyte in all matrices.
[#] Values based on total number of samples.
[*] Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.
n = number of field trials.
[1] In the duplicate samples of leaf lettuce (29-30 day PBI) collected from Trial 01NC, residues of tioxazafen were 0.0025 ppm (LOQ) and residues of benzamidine were <0.0025 ppm (<LOQ) in one sample, and in the other sample residues of tioxazafen were 0.0060 pm and residues of the metabolite benzamidine were <0.0025 ppm (<LOQ). Residues of each analyte were <0.0025 ppm (<LOQ) in the duplicate leaf lettuce (29-30 day PBI) samples collected from Trial 02CA.
[2] In the duplicate samples of radish tops (29-30 day PBI) collected from Trial 01NC, residues of tioxazafen and the metabolite benzamidine were each <0.0025 ppm in one sample, and in the other sample residues of tioxazafen were <0.0025 (<LOQ) and residues of the metabolite benzamidine were 0.0030 ppm. In the duplicate samples of radish tops (29-30 day PBI) collected from Trial 02CA, residues of tioxazafen were <0.0025 ppm (<LOQ) in both samples and residues of the metabolite benzamidine were 0.0042 ppm in one sample and in the other sample were 0.0033 ppm.

Based on the results of the field accumulation study, a plant-back interval of 30 days is required for all crops except the label crops of corn and soybean.

PROCESSED FOOD AND FEED - COTTON	PMRA # 2483119
Test Site	Field trials were conducted in 2013 in the United States in NAFTA Growing Regions 2 (SC and GA; 2 trials), 4 (MS, MO, LA; 3 trials), 6 (TX; 2 trials), 8 (TX and OK; 4 trials), and 10 (CA; 1 trial) for a total of twelve trials. The above trial count reflects one pair of trials determined to be replicate trials.
Treatment	Seed treatment
Rate	At each site three plots were established: Treatment 1 (control), Treatment 2 (nominal rate 1.0 mg a.i./seed) and Treatment 3 (nominal rate 2.0 mg a.i./seed).
End-use product/formulation	MON 102119 (47.3-47.8% a.i.)/Suspension concentrate (SC)
Preharvest interval	The entire Treatment 1 and 3 plots were harvested to provide bulk seed samples for processing. Samples of cotton seed were harvested 146-183 days after planting (DAP) by hand and/or picker and stripper equipment. Samples were ginned at field sites within 26 hours of harvest to produce samples of undelinted cotton seed from all trials.
Processed Commodity	After analysis of all undelinted cotton seed field trial samples (not including the bulk samples) from all sites, it was determined that processing was not necessary because there were no quantifiable residues (<0.0025 ppm per analyte) of tioxazafen or benzamidine (tioxazafen equivalents) in/on any undelinted cotton seed sample.

PROCESSED FOOD AND FEED – FIELD CORN	PMRA # 2483117
Test Site	Bulk grain samples from Treatment 1 (control) and Treatment 4 (nominal 2.0 mg a.i./seed) from the corn field trial study were to be used for processing. Larger size plots for these treatments were established at two sites (10IA and 16NE) of the field residue trial program for the purpose of generating sufficient grain for processing. However, prior to harvest it was determined that there would not be enough grain produced from these two sites for processing. As a result, the protocol was amended and after normal harvest, all available grain (bulk) was taken from the Treatment 1 (control) and Treatment 4 plots at each site. Grain (bulk) from several sites was composited to produce Processing Sample 1 (04IN, 09IA, 11IA, and 16NE composite; 225.0 kg) and Processing Sample 2 (20WI, 03MI, and 13IA composite, 264.9 kg), and the corresponding control samples (406.4 kg and 235.9 kg).
Treatment	Seed treatment
Rate	2.0 mg a.i./seed (nominal)
End-use product/formulation	MON 102116 (48.7% w/w a.i.)/Suspension concentrate (SC)
Preharvest interval	126-174 days after planting (DAP)
Processed Commodity	The corn grain RAC (raw agricultural commodity) was processed into grits, meal, flour, and RBD (refined, bleached and deodorized) oil by dry milling, and into starch and RBD oil by wet milling. Given that residues each of tioxazafen and the metabolite benzamidine (determined as tioxazafen equivalents) were each <LOQ (<0.0025 ppm per analyte) in both the corn grain RAC and processed fractions (grits, meal, flour, RBD oil and starch), processing factors could not be determined.
PROCESSED FOOD AND FEED - SOYBEAN	PMRA # 2483118
Test Site	Bulk seed samples from Treatment 1 (control) and Treatment 3 (nominal 1.0 mg a.i./seed) from the soybean field trial study with the highest residues (06LA, NAFTA Growing Region 4 and 10IL, NAFTA Growing Region 5) were to be used for processing.
Treatment	Seed treatment
Rate	1.0 mg a.i./seed (nominal)
End-use product/formulation	MON 102119 (47.3% w/w a.i.)/Suspension concentrate (SC)
Preharvest interval	128- days after planting DAP at the 06LA site and 113-DAP at the 10IL site.
Processed Commodity	The soybean seed RAC (raw agricultural commodity) was processed into meal, toasted meal, crude oil, crude lecithin, degummed oil and RBD (refined, bleach and deoderized) oil. The processing factors for tioxazafen could not be determined as residues of tioxazafen were <LOQ (<0.0025 ppm) in all samples of soybean seed RAC and processed fractions. Residues of the metabolite benzamidine concentrated only in meal (median processing factor =1.4x) and toasted meal (median processing factor = 1.6x).

LIVESTOCK FEEDING – Dairy cattle	PMRA # 2483123

Tioxazafen (MON 102100) was administered orally via gelatin capsule to eighteen Holstein dairy cows (*Bos taurus*) for twenty-eight consecutive days. Dosing (average) was made at 0, 0.12, 0.60, 3.00 and 12.01 mg/kg feed (dry matter basis) (ppm). The dose levels of 0.12, 0.60, 3.00 and 12.01 ppm represent 1.2x, 6x, 30x and 120x, respectively, the estimated dietary burden for dairy cattle. There were 3 animals assigned to each of the control, 1x, 6x, and 30x treatment groups, and six animals were assigned to the 120x group, three of which were selected for the depuration phase. For the 10-day depuration phase, milk samples were collected on Study Days 30, 33 and 37, and tissue samples were collected on Study Days 31, 34 and 38.

Residues of tioxazafen were <LOQ (<0.01 ppm) in whole milk, skim milk and cream samples collected on Study Days 22, 25 and 28 for both the 3.00 and 12.01 ppm feeding levels. As such, concentration factors could not be determined for tioxazafen in skim milk and cream. Residues of benzamidine and 2-thenoylglycine did not concentrate in samples of skim milk or cream with concentration factors ranging from 1.0-1.2x.

By the end of the depuration phase, residues of each analyte were non-quantifiable in/on each cattle matrix.

The estimated dietary burdens (DBs) were calculated using an Excel-based spreadsheet: 0.0009 ppm for beef cattle, 0.1 ppm for dairy cattle and 0.007 ppm for swine.

The anticipated residues (tioxazafen + benzamidine; residue definition for enforcement and risk assessment) were calculated using the highest residues from the 12.01 ppm feeding level:

- [Transfer coefficient (highest residues ÷dose)] × [Dietary Burden (DB)]

Commodity	Feeding Level (ppm)	Highest Residues (Tioxazafen equivalents; ppm)				Dietary Burden (DB; ppm)	Anticipated Residues (Tioxazafen + Benzamidine; ppm)	
		Tioxazafen	Benzamidine	2-Thenoylglycine	Benzonitrile		Enforcement + Risk Assessment	
							Dairy Cattle	Swine
Whole milk	12.01	<0.01	0.1060	0.0304	NA	0.1 [dairy cattle]; 0.007 [swine]	9.7×10^{-4}	Not applicable
Skim milk		<0.01	0.0921	0.0216	NA		8.5×10^{-4}	
Cream		<0.01	0.0837	0.0168	NA		7.8×10^{-4}	
Fat		<0.01	0.0495	NA	<0.025		5×10^{-4}	3.5×10^{-5}
Liver		<0.01	0.163	<0.06	NA		1.4×10^{-3}	1.0×10^{-4}
Kidney		<0.01	0.194	0.117	NA		1.7×10^{-3}	1.2×10^{-4}
Muscle		<0.01	0.0410	NA	NA		4.2×10^{-4}	2.9×10^{-5}
Whole milk	3.00	NA	0.0350	<0.01	NA			
Skim milk		NA	0.0283	<0.01	NA			
Cream		NA	0.0257	<0.01	NA			
Fat		NA	0.0179	NA	NA			
Liver		NA	0.0541	NA	NA			
Kidney		NA	0.0668	0.0484	NA			
Muscle		NA	0.0141	NA	NA			
Whole milk	0.60	NA	<0.01	NA	NA			
Skim milk		NA	NA	NA	NA			
Cream		NA	NA	NA	NA			
Fat		NA	0.0114	NA	NA			

Liver		NA	0.0185	NA	NA			
Kidney		NA	0.0177	<0.025	NA			
Muscle		NA	<0.01	NA	NA			
Whole milk	0.12	NA	<0.01	NA	NA			
Skim milk		NA	NA	NA	NA			
Cream		NA	NA	NA	NA			
Fat		NA	<0.01	NA	NA			
Liver		NA	<0.01	NA	NA			
Kidney		NA	<0.01	<0.025	NA			
Muscle		NA	<0.01	NA	NA			

NA = Not analyzed.

Note: Residues of the metabolite benzonitrile were analyzed in fat only, and residues of the metabolite 2-thenoylglycine were analyzed in only milk, kidney and liver based on the results of the goat metabolism study (PMRA # 2483529).

LIVESTOCK FEEDING – Laying hens	PMRA # 2483141

Tioxazafen was administered orally via gelatin capsule to seventy two white leghorn hens (*Gallus gallus domesticus*) for 28 consecutive days. Dosing (average) was made at 0, 0.81, 4.0, 20.8 and 79.1 mg/kg feed (dry matter basis) (ppm). The dose levels of 0.81, 4.0, 20.8 and 79.1 ppm represent 101x, 500x, 2600x and 9888x, respectively, the estimated dietary burden to poultry. For the depuration phase, birds in the 101x group were sacrificed on Study Days 31, 34 and 38.

In egg yolks, residues of tioxazafen and the metabolite benzamidine each concentrated (2.9-3.6x and 2.6-3.1x, respectively) compared to whole eggs. There were no quantifiable residues of each analyte in egg whites; as such concentration factors could not be determined.

By the end of the depuration phase, only residues of the metabolite benzamidine were quantifiable and only in liver (0.0649 ppm).

The anticipated residues (tioxazafen + benzamidine; residue definition for enforcement and risk assessment) were calculated as using the highest residues from the 79.1 ppm feeding level:

- [Transfer coefficient (highest residues ÷dose)] × [Dietary Burden (DB)]

Commodity	Feeding Level (ppm)	Highest Residues (Tioxazafen equivalents; ppm)			Dietary Burden (DB; ppm)	Anticipated Residues (Tioxazafen + Benzamidine; ppm)
		Tioxazafen	Benzamidine	Benzonitrile		Enforcement + Risk Assessment
Whole Egg	79.1	0.0239	0.0273	NA	0.008	5.0×10^{-6}
Egg Yolk		0.0726	0.0738	NA		1.4×10^{-5}
Egg White		<0.01	<0.01	NA		2.0×10^{-6}
Fat		0.3618	<0.01	0.0645		3.8×10^{-5}
Liver		<0.01	1.030	NA		1.0×10^{-4}
Muscle		<0.01	0.0177	NA		2.8×10^{-6}
Whole Egg	20.8	<0.01	0.0111	NA		
Egg Yolk		0.0137	0.0248	NA		
Egg White		NA	NA	NA		
Fat		0.0519	NA	<0.025		
Liver		<0.01	0.0787	NA		
Muscle		NA	<0.01	NA		
Whole Egg	4.0	NA	<0.01	NA		
Egg Yolk		NA	NA	NA		

Egg White		NA	NA	NA		
Fat		0.0106	NA	<0.025		
Liver		<0.01	0.0148	NA		
Muscle		NA	<0.01	NA		
Whole Egg	0.81	NA	NA	NA		
Egg Yolk		NA	NA	NA		
Egg White		NA	NA	NA		
Fat		<0.01	NA	<0.025		
Liver		<0.01	<0.01	NA		
Muscle		NA	<0.01	NA		

NA = Not analyzed.
Note: Residues of the metabolite benzonitrile were analyzed in fat only based on the results of the hen metabolism study (PMRA # 2483141).

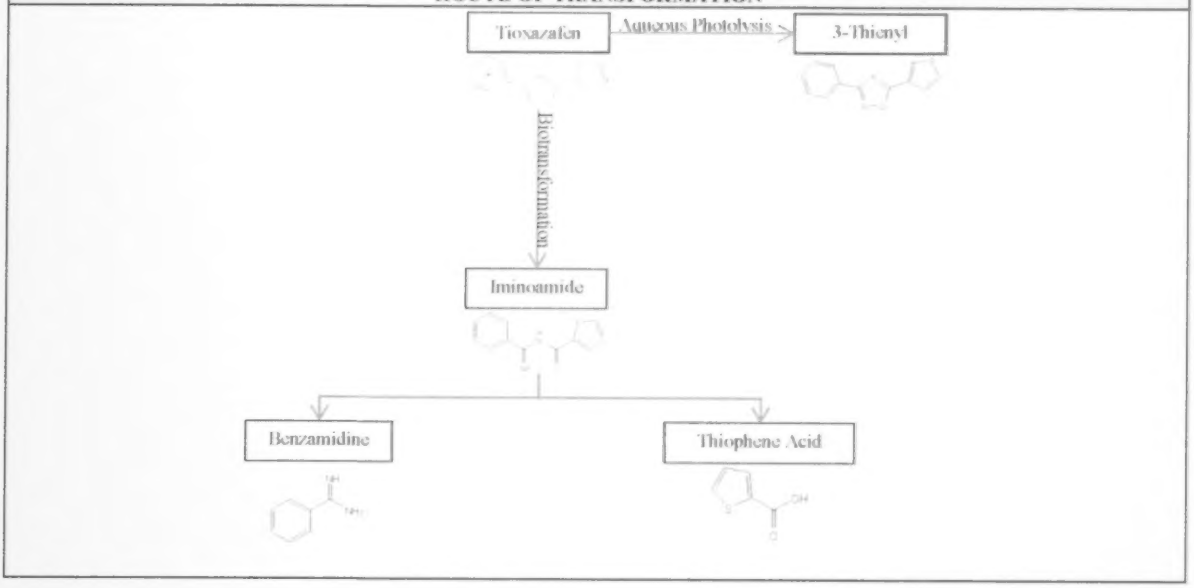
Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

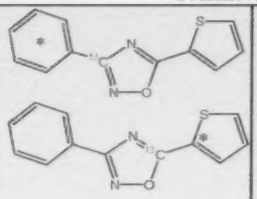
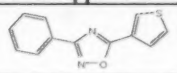
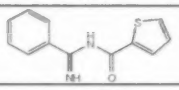
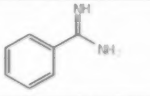
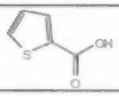
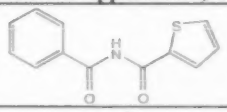
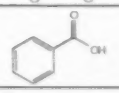
PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT Primary crops (seed treatment: corn, cotton and soybean) Rotational crops		Tioxazafen and the metabolite benzamidine	
RESIDUE DEFINITION FOR RISK ASSESSMENT Primary crops Rotational crops		Tioxazafen and the metabolite benzamidine	
METABOLIC PROFILE IN DIVERSE CROPS		The profile in diverse crops cannot be determined because only oilseed crops (cotton and soybean) and a cereal crop (corn) were investigated.	
ANIMAL STUDIES			
ANIMALS		Ruminant and Poultry	
RESIDUE DEFINITION FOR ENFORCEMENT		Tioxazafen and the metabolite benzamidine	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Tioxazafen and the metabolite benzamidine	
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)		Similar metabolic profile in goat, rat and hen.	
FAT SOLUBLE RESIDUE		Yes	
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Alone	Food and Water
Basic chronic non-cancer dietary exposure analysis ADI = 0.05 mg/kg bw/day Estimated chronic drinking water concentration = 0.12 □g/L	All infants < 1 year	0.8	0.8
	Children 1–2 years	2.1	2.2
	Children 3 to 5 years	1.3	1.3
	Children 6–12 years	0.8	0.8
	Youth 13–19 years	0.4	0.4
	Adults 20–49 years	0.3	0.3
	Adults 50+ years	0.2	0.3
	Females 13-49 years	0.3	0.3
	Total population	0.4	0.4

	POPULATION	ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)	
		Food Alone	Food and Water
Basic acute dietary exposure analysis, 95th percentile ARfD = 0.8 mg/kg bw Estimated acute drinking water concentration = 1.1 □g /L	All infants < 1 year	0.17	0.18
	Children 1–2 years	0.28	0.28
	Children 3 to 5 years	0.17	0.17
	Children 6–12 years	0.10	0.11
	Youth 13–19 years	0.06	0.06
	Adults 20–49 years	0.04	0.05
	Adults 50+ years	0.04	0.04
	Females 13-49 years	0.04	0.05
	Total population	0.08	0.09
Basic cancer dietary exposure analysis $q_1^* = 3.41 \times 10^{-3}$ (mg/kg bw/day)$^{-1}$ Estimated chronic drinking water concentration = 0.12 □g/L	POPULATION	ESTIMATED LIFETIME CANCER RISK	
		Food Alone	Food and Water
	Total population	7×10^{-7}	7×10^{-7}

Table 8 Route of Transformation and Transformation Products in Environmental Fate Studies

Code and Chemical name	Chemical structure	Study	max %AR[1] (day)	%AR[1] at Study End (study length)[2]
ROUTE OF TRANSFORMATION				



Code and Chemical name	Chemical structure	Study	max %AR[1] (day)	%AR[1] at Study End (study length)[2]
PARENT				
MON 102100 **Tioxazafen** (3-phenyl-5-(2-thienyl)-1,2,4-oxadiazole) CAS: 330459-31-9				
MAJOR (>10% of the applied dose) TRANSFORMATION PRODUCTS				
MON 102130 (3-Thienyl 102100) 3-phenyl-5-(3-thienyl)-1,2,4-oxadiazole		Soil photolysis	3.0 (15)	3.0 (15)
		Aqueous photolysis	95.2 (0.42)	91.9 (1)
MON 102100 Iminoamide [*N*-(iminophenylmethyl)-2-thiophenecarboxamide]		Anaerobic soil	8.9 (29)	2 (120)
		Aerobic aquatic	40 (7)	nd (129)
		Anaerobic aquatic	41.3 (7)	nd (129)
Benzamidine CAS: 618-39-3		Anaerobic soil	27.7 (90)	25.7 (120)
		Aerobic aquatic	35.5 (14)	10.1 (129)
		Anaerobic aquatic	65.8 (14)	30.3 (127)
		Field studies (ppm)	0.0117 (92)	0.0015 (388)
Thiophene acid [2-thiophenecarboxylic acid]		Anaerobic soil	13.6 (59)	nd (120)
		Aerobic aquatic	28.6 (14)	nd (59+)
		Anaerobic aquatic	5.1 (7)	2.2 (28)
Unextracted Residues		Aerobic soil	-	51.8 (121)
		Anaerobic soil	-	57.3 (120)
		Aerobic aquatic	-	69.0 (129)
		Anaerobic aquatic	-	67.3 (127)
CO_2		Aerobic soil	-	19.7 (121)
		Anaerobic soil	-	13 (120)
		Aerobic aquatic	-	73.1 (129)
MINOR (<10% of the applied dose) TRANSFORMATION PRODUCTS				
MON 102100 Imide [*N*-benzoyl-2-thiophenecarboxamide]		Aerobic soil	0.3 (83)	nd (123)
		Anaerobic soil	0.9 (90)	0.7 (120)
		Aerobic aquatic	1 (7)	nd (30)
		Anaerobic aquatic	2.4 (14)	1.7 (28)
Benzoic acid		Anaerobic soil	0.5 (59;90)	nd (120)

[1] %AR: percent of applied radioactivity

[2] at study end (study length): %AR at the end of the study and study length or first time where an undetected value (nd) is observed

Table 9 Fate and behaviour in the terrestrial and aquatic environments

Study type	Test material	Value[1]	Classification/ Interpretation	Major transformation products	References[2] (PMRA #)
Abiotic transformation					
Hydrolysis	Tioxazafen	1d, pH 4, 7, and 9 at 50°C Stable	Not an important route of transformation	NA	2483524
Phototransformation - soil	Tioxazafen	Moist soil, continuous lightning Stable	Not an important route of transformation	NA	2483580
Phototransformation - water	Tioxazafen	pH 7, sterile, continuous lightning DT_{50}=2.26 h	Not an important route of degradation of	3-Thienyl 102100[3]	2483549

Study type	Test material	Value[1]	Classification/ Interpretation	Major transformation products	References[2] (PMRA #)
		Tioxazafen + 3-Thienyl 102100 Stable	tioxazafen		
Phototransformation - air	Tioxazafen is unlikely to volatilize based on its vapor pressure (5.82×10^{-7} mm Hg at 25°C) and Henry's Law constant ($1.41 \times 10\text{-}7$ atm*m^3/mol at 25°C)				
Biotransformation					
Soil -aerobic	Tioxazafen	123d, four soils; pH 5.7-7.5, %OM 2.2 – 7.6, 20°C Manning Sandy Loam DT50: 21.8 d; DT90: 132 d (DFOP – combined labels; representative half-life for modelling purposes: 48.1 d) Hoyleton Silt Loam DT50: 53.2 d; DT90: 233 d (IORE – combined labels; representative half-life for modelling purposes: 70.3 d) Webster Sandy clay Loam DT50: 140 d; DT90: 527 d (DFOP – combined labels; representative half-life for modelling purposes: 167 d) Bearnes-Svea Clay Loam DT50: 237 d; DT90: 940 d (DFOP – combined labels; representative half-life for modelling purposes: 303 d) 90th percentile confidence bound on mean of four combined residue half-life values: 242 d	Slightly persistent to persistent Biotransformation in aerobic soil is a route of dissipation for tioxazafen.	NA	2483544
Soil -anaerobic	Tioxazafen	120d, four soils; pH 5.7-7.7, %OM 2.1 – 5.7, 20°C Manning Sandy Loam DT50: 21.7 d; DT90: 72 d (SFO – combined labels) Hoyleton Silt Loam DT50: 128 d; DT90: 427 d (SFO – combined labels) Webster Sandy clay Loam DT50: 465 d; DT90: 1 545 d (SFO – combined labels) Bearnes-Svea Clay Loam DT50: 500 d; DT90: 1 660 d (SFO – combined labels)	Slightly persistent to persistent Biotransformation in anaerobic soil is a route of dissipation for tioxazafen.	Benzamidine Thiophene acid Combined residues[1] DT50: 56.4 d	2483585
Water -aerobic	Tioxazafen	129d, river and lake water, %OM 0.71-5.6, 20°C; pH 8.2-8.3 Goose River DT50: 4.37 d; DT90: 14.5 d (SFO – combined labels) Golden Lake DT50: 5.93 d; DT90: 19.7 d (SFO – combined labels)	Non-persistent	MON 102100 Iminoamide DT50: 3.02–5.07 d Benzamidine DT50: 55.2-78.7d Thiophene acid DT50: 13.1-14.1d	2483492

Study type	Test material	Value[1]	Classification/ Interpretation	Major transformation products	References[2] (PMRA #)
				Combined residues[4] DT50: 37.8-86.1d	
Water -anaerobic	Tioxazafen	99d, river and lake water, %OM 1.3-7.8, 20°C; pH 7.7-8.1 Goose River DT50: 4.37 d; DT90: 14.5 d (SFO – combined labels) Golden Lake DT50: 5.98 d; DT90: 19.9 d (SFO – combined labels)	Non-persistent	MON 102100 Iminoamide DT50: 6.64-12d Benzamidine DT50: 97.9-256d Combined residues[4] DT50: 51.3-183d	2483496
Mobility					
Adsorption/ desorption	Tioxazafen	Six soils (pH 5.3-7.3, 0.43-3.3%OC) Koc(20th centile) = 3146 Loamy Sand Koc = 5371 Silt Loam Koc = 2996 Sandy Clay Loam Koc = 10318 Clay Loam Koc = 3146 Sandy Loam Koc= 3189 - 4808	Slight mobility to Immobile	NA	2483517
Volatilization	Tioxazafen is unlikely to volatilize from water and moist soil based on its vapor pressure (5.82×10^{-7} mm Hg at 25°C) and Henry's Law constant ($1.41 \times 10\text{-}7$ atm*m^3/mol at 25°C)				
Field Study of dissipation	EP	Four soils, pH 5.0 - 8.6, %OM 0.09-4.1, Study duration: 540d[5] **Seed treatments:** Manitoba (Canada) DT50: 220d; DT 90: 1500d (DFOP – combined labels; representative half-life: 552 d) Illinois (USA) DT50: 44.7d; DT 90: 149 (SFO – combined labels, representative half-life = DT50) Nebraska (USA) DT50: 26.9d; DT 90: 314d (IORE – combined labels; representative half-life: 94.6 d) Georgia (USA) DT50: 94.3d; DT 90: 313 (SFO – combined labels, representative half-life = DT50) **In furrow applications:**	Slightly persistent to persistent	Benzamidine	2483138

Study type	Test material	Value[1]	Classification/ Interpretation	Major transformation products	References[2] (PMRA #)
		Manitoba (Canada) DT50:73.1d; DT90: 729d (IORE – combined labels; representative half-life: 219 d) Illinois (USA) DT50: 36.7d;DT90: 530d (DFOP – combined labels; representative half-life: 220 d) Nebraska (USA) DT50: 101d; DT 90: 336d (SFO – combined labels, representative half-life = DT50) Georgia (USA) DT50: 40.1d; DT 90: 332d (IORE – combined labels, representative half-life: 100)			
Bioconcentration/Bioaccumulation					
Bioconcentration[6]	Tioxazafen	0.6 µg/L BCFss = 1321 BCFss,g = 2836 BCFk = 2048 BCFk,l = 1340 BCFk,g = 4330 BCFk,g,l = 2833 6 µg/L BCFss = 1156 BCFss,g = 2706 BCFk = 1701 BCFk,l = 1094 BCFk,g = 4418 BCFk,g,l = 2699	Considered bioaccumulative, but does not meet Track-1 bioaccumulation criterion.	NA	2483468

[1] Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel.
[2] USEPA classification, where applicable
[3] 3-thienyl TIOXAZAFEN (also MON 102130) is an isomer of the parent tioxazafen (MON 102100)
[4] Combined residues include tioxazafen, MON 102100 iminoamide and benzamidine
[5] Only the soil in Manitoba was in a Canadian-relevant ecoregion. The plots in Illinois were accepted as being a close-equivalent to Ontario. Plots in Nebraska and Georgia are not in Canadian-relevant ecoregions and are not considered as close-equivalent as well.
[6] Bioconcentration factors (BCF) are provided at the end of the uptake phase, assuming steady state (BCFss), and based on kinetic analysis (BCFk) of both the uptake and depuration phases. Correction of kinetic BCFs for growth dilution (BCFkg and BCFss,g) was obtained using weight data (weight of tioxazafen in fish) instead of concentration (weight of tioxazafen per kg of fish tissue) as first order kinetic did not clearly apply to fish growth. BCFs were normalized to a 5% lipid content in fish tissue (BCFkl)

Table 10 Toxicity to non-target terrestrial species

Species	Exposure	Test material	Value	Classification[1]	Reference (PMRA #)
Invertebrates					
Adulte bee (*Apis mellifera*)	Acute oral	Tioxazafen	48-h LC_{50} > 0.41 $\mu g_{a.i.}$/bee	No toxicity at the highest concentration tested	2483516
Adulte bee (*Apis mellifera*)	Acute contact	Tioxazafen	48-h LC_{50} > 100 $\mu g_{a.i.}$/bee	Practically non-toxic	2483523
Earthworm (*Eisenia andrei*)	Chronic	Tioxazafen	**Survival** NOEC = 1000 $mg_{a.i.}/kg_{dry\ soil}$	No effects on survival at any concentration	2483561

Species	Exposure	Test material	Value	Classification[1]	Reference (PMRA #)
			Growth NOEC = 308.6 $mg_{a.i.}/kg_{d.sed}$ **Reproduction** NOEC < 95.3 $mg_{a.i.}/kg_{d.sed}$	tested. Reproductive effects at the lowest concentration tested.	
Birds					
Bobwhite quail (*Colinus virginianus*)	Acute oral	Tioxazafen	LD50: 4500 $mg_{a.i.}/kg_{bw}$	Practically non-toxic	2483519
Canary (*Serinus canaria*)	Acute oral	Tioxazafen	LD50: 315 $mg_{a.i.}/kg_{bw}$	Moderately toxic	2483521
Bobwhite quail (*Colinus virginianus*)	Dietary	Tioxazafen	8-d LC50: 4645 $mg_{a.i.}/kg_{diet}$ 8-d LD50: 835 $mg_{a.i.}/kg_{bw}/d$	Slightly toxic	2483520
Mallard duck (*Anas platyrhynchos*)	Dietary	Tioxazafen	8-d LC50: 4085 $mg_{a.i.}/kg_{diet}$ 8-d LD50: 907 $mg_{a.i.}/kg_{bw}/d$	Slightly toxic	2483525
Bobwhite quail (*Colinus virginianus*)	Reproduction	Tioxazafen	NOEC: 976 $mg_{a.i.}/kg_{diet}$ NOEL: 84.86 $mg_{a.i.}/kg_{bw}/d$	No effects at the highest concentration tested.	2483543
Mallard duck (*Anas platyrhynchos*)	Reproduction	Tioxazafen	NOEC: 243 $mg_{a.i.}/kg_{diet}$ NOEL: 37.85 $mg_{a.i.}/kg_{bw}/d$	Observed effects were eggs laid/pen, viable embryos/egg set, live embryos/egg set, hatchlings/egg set, 14d survivors/egg set, eggshell thickness, and 14d survivor weight.	2483542
Mammals					
Rat	Acute oral	Tioxazafen	LD50 > 5,000 $mg_{a.i.}/kg_{bw}$	Practically non-toxic	2483491
	Reproduction	Tioxazafen	NOEL = 60 $mg_{a.i.}/kg_{bw}/d$	No effects noted at the highest dose tested	2483486
Plants					
Seedling emergence (*4 monocots, 6 dicots*)		MON 102133	ER_{25} >0.36 $kg_{a.i.}/ha$ NOER: 0.31 $kg_{a.i.}/ha$	No classification	2483139

Table 11 Toxicity to non-target Aquatic species

Species	Exposure	Test material	Value	Classification[1]	Reference (PMRA #)
Midge Larvae (*Chironomus tentans*)	Acute	Tioxazafen	10-d LC50: 233 $mg_{a.i.}/kg_{sediment}$ 10-d LC50: 1.17 $mg_{a.i.}/L_{pore\ water}$	The pore water concentrations reached an equilibrium concentration near the limit of solubility (1.24 mg/L)	2483533
Crustacean (*Daphnia magna*)	Acute	Tioxazafen	48-h EC50 >1.2 $mg_{a.i.}/L$	No more than moderately toxic	2483522
			48-h NOEC = 0.42 $mg_{a.i.}/L$ 48-h LOEC = 0.75 $mg_{a.i.}/L$	Sublethal effect: lethargy	
		MON 102130	48-h EC50 = 0.834 $mg_{a.i.}/L$	Highly toxic	2483562
Crustacean (*Daphnia magna*)	Chronic	Tioxazafen	21-d NOEC: 0.0059 $mg_{a.i.}/L$ 21-d LOEC: 0.014 $mg_{a.i.}/L$	No classification	2483540
Rainbow trout (*Oncorhynchus mykiss*)	Acute	Tioxazafen	96-h LC50: 0.0911 $mg_{a.i.}/L$	Very highly toxic	2483526
		MON 102130	96-h LC50: 0.037 $mg_{a.i.}/L$	Very highly toxic	2483485
		MON 102133	96-h LC50: 0.083 $mg_{a.i.}/L$	Very highly toxic	2483567
Bluegill sunfish (*Lepomis macrochirus*)	Acute	Tioxazafen	96-h LC50: 0.51 $mg_{a.i.}/L$	Very highly toxic	2483518
Fathead Minnow (*Pimephales promelas*)	ELS	Tioxazafen	33-d NOEC: 0.0094 $mg_{a.i.}/L$	Very highly toxic	2483546
Freshwater algae (*Pseudokirchneriella subcapitata*)	Acute	Tioxazafen	96-h EbC50: 0.7114 $mg_{a.i.}/L$	No classification	2483537

Species	Exposure	Test material	Value	Classification[1]	Reference (PMRA #)
Freshwater diatom (*Navicula pelliculosa*)	Acute	Tioxazafen	96-h IC50: 0.1253 $mg_{a.i.}/L$	No classification	2483538
		MON 102130	IC50 > 0.255 $mg_{a.i.}/L$ NOEC: 0.123 $mg_{a.i.}/L$	No classification	2483563
Duckweed (*Lemna gibba*)	Acute	Tioxazafen	7-d IC50 > 0.954 $mg_{a.i.}/L$ 7-d IC05 = 0.508 $mg_{a.i.}/L$	No classification	2483535
Marine amphipod (*Leptocheirus plumulosus*)	Acute	Tioxazafen	10-d LC50 3.2 $mg_{a.i.}/kg_{sediment}$ 128 $mg_{a.i.}/kg_{OC}$ 0.33 $mg_{a.i.}/L$	No classification	2483534
Mysid shrimp (*Americamysis bahia*)	Acute	Tioxazafen	96-h LC50: 0.337 $mg_{a.i.}/L$	No classification	2483484
Mysid shrimp (*Americamysis bahia*)	Chronic	Tioxazafen	28-d NOEC: 0.044 $mg_{a.i.}/L$	No effects at the highest concentration tested	2483541
Eastern Oyster (*Crassostrea virginica*)	Acute	Tioxazafen	96-h EC50: > 0.183 $mg_{a.i.}/L$	No classification	2483483
			NOEC < 0.019 $mg_{a.i.}/L$	Reduction in shell thickness	
Sheepshead minnow (*Cyprinodon variegatus*)	Acute	Tioxazafen	96-h LC50 > 0.084 $mg_{a.i.}/L$	Highly toxic; 35% mortality at the highest concentration tested	2483527
Marine diatom (*Skeletonema costatum*)	Acute	Tioxazafen	96-h IC50: 0.6203 $mg_{a.i.}/L$	No classification	2483539

Table 12 Risk assessment of oral exposure to pollen and nectar from seed treatment of tioxazafen (MON102133 Nematicide SC Seed Treatment) to honey bees (*Apis mellifera*)

Ecotoxicity endpoint	Total pollen and nectar Consumption[1]	Pollen and nectar residues	Estimated exposure from corn pollen[4]	RQ	LOC Exceeded?[5]
Acute oral 48-h LC50 : > 0.41 µg a.i./bee (PMRA# 2483516)	0.292 g/bee/day	Tier 1 [Default Value][2] 1µg a.i./g pollen and nectar	0.292 µg a.i./bee/day	**0.7**	Yes
		Tier 2 [LOD from residue Data][3] ≤ 0.00021 µg a.i./g pollen and nectar	≤ 0.00021 µg a.i./bee/day	≤ 0.0005	No

[1] The pollen consumption value selected for this risk assessment is the highest total consumption among adult workers and larvae (sum of pollen and nectar consumption), from U.S. EPA *et al.* (2014).

[2] Default value for pollen and nectar residues in plant grown from treated seeds as per U.S. EPA *et al.* (2014).

[3] No residues of tioxazafen were detected in pollen and nectar of plants grown from treated seeds in PMRA# 2588323; therefore, the LOD was used for risk assessment purposes.

[4] The estimated exposure is calculated as follows:
Exposure (µg a.i./bee/day) = Pollen and nectar consumption (g /bee/day) × pollen and nectar residues (µg a.i./g pollen and nectar)

[5] The level of concern (LOC) for bees is set to 0.4.

Table 13 EEC and risk to non-target terrestrial organisms except bees, birds and mammals

Reference	Description	Parameter			On-field EEC		Level of concern	RQ
Based on Screening Level EECs								
2483139	Vascular plants	NOER	=	0.31 kg a.i./ha	125	g a.i./ha[1]	1	0.4
2483561	Chronic earthworm	NOEC	<	95.3 mg a.i./kg_{soil}	0.06	mg a.i./kg_{soil}[2]	1	<0.001

[1] highest label rate of 0.25 mg a.i./seed (soybeans) and a planting density of 500 000 seeds per hectare.

[2] highest label rate of 125 g a.i./ha, incorporated into the first 15 cm of soil and assuming a soil density of 1.5 g/cm^3.

Table 14 Risk to birds and mammal from the use of treated soybeans

Study Endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)[1]	RQ[1]	Number of seeds needed to reach endpoint[1]	Area required (m2)[2]			
					No Drilling		Precision drilling	
					min	max	min	max
Small bird (0.02 kg)								
Acute	31.50	470	15	2.5	0.03	0.08	5.4	16
Dietary	83.50	470	5.6	6.7	0.07	0.21	14	42
Reproduction	37.85	470	12	3.0	0.03	0.10	6.5	19
Medium bird (0.10 kg)								
Acute	31.50	370	12	13	0.14	0.40	27	80
Dietary	83.50	370	4.4	33	0.36	1.1	72	213
Reproduction	37.85	370	9.7	15	0.16	0.48	32	97
Large bird (1.00 kg)								
Acute	31.50	108	3.4	126	1.4	4.0	270	804
Dietary	83.50	108	1.3	334	3.6	10.6	716	2131
Reproduction	37.85	108	2.8	151	1.6	4.8	325	966
Small mammals (0.015 kg)								
Acute	500.00	269	0.5	30	0.32	0.96	64	191
Reproduction	60.00	269	4.5	3.6	0.04	0.11	7.7	23
Medium mammals (0.035 kg)								
Acute	500.00	231	0.5	70	0.75	2.2	150	447
Reproduction	60.00	231	3.8	8.4	0.09	0.27	18	54
Large mammals (1.00 kg)								
Acute	500.00	127	0.3	2000	21	64	4290	12759
Reproduction	60.00	127	2.1	240	2.6	7.7	515	1531

[1] Based on a label rate of 0.25 mg a.i./seed; does not account for feeding preferences, soybeans not being very attractive to birds.
[2] The area required for a bird or mammal to find enough exposed seeds to reach selected endpoint. Does not consider birds or mammals eating buried seeds.

Table 15 Risk to birds and mammal from the use of treated corn seeds

Study Endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)[1]	RQ[1]	Number of seeds needed to reach endpoint[1]	Area required (m^2)[2]			
					No Drilling		Precision drilling	
					min	max	min	max
Small bird (0.02 kg)								
Acute	31.50	419	13	1.3	0.12	0.23	24	45
Dietary	83.50	419	5.0	3.3	0.32	0.60	63	120
Reproduction	37.85	419	11	1.5	0.14	0.27	29	54
Medium bird (0.10 kg)								
Acute	31.50	329	10	6.3	0.60	1.13	119	226
Dietary	83.50	329	3.9	16.7	1.58	3.00	316	600
Reproduction	37.85	329	8.7	7.6	0.72	1.36	143	272
Large bird (1.00 kg)								
Acute	31.50	96	3.0	63	5.97	11.32	1193	2264
Dietary	83.50	96	1.1	167	15.81	30.01	3163	6002
Reproduction	37.85	96	2.5	76	7.17	13.60	1434	2721
Small mammals (0.015 kg)								
Acute	500.00	239	0.5	15	1.42	2.70	284	539
Reproduction	60.00	239	4.0	1.8	0.17	0.32	34	65
Medium mammals (0.035 kg)								
Acute	500.00	206	0.4	35	3.31	6.29	663	1258
Reproduction	60.00	206	3.4	4.2	0.40	0.75	80	151
Large mammals (1.00 kg)								
Acute	500.00	113	0.2	1000	94.70	179.69	18939	35939
Reproduction	60.00	113	1.9	120	11.36	21.56	2273	4313

[1] Based on the label rate of 0.5 mg a.i./seed and the highest number of seeds per kg (3 300 seeds/kg)
[2] The area required for a bird or mammal to find enough exposed seeds to reach selected endpoint. Does not consider birds or mammals eating buried seeds; current practice is to plant corn using precision drilling.

Table 16 Major surface water model inputs for Level 1 assessment of tioxazafen

Type of Input	Parameter	Value		
Application Information	Crop(s) to be treated	Corn and soybeans		
	Maximum application rate per year originally considered (g a.i./ha)	250[1]		
	Method of application	CAM 8 (buried and covered with soil) at depth of 0.75 to 3")		
Environmental Fate Characteristics	**Compound**	**Tioxazafen**	**3-thienyl 102100**	**IMI+BEN**
	Hydrolysis half-life at pH 7 (days)	Stable	Stable	Stable
	Photolysis half-life in water (days)	0.188	11.99	Stable
	Adsorption K_{oc} (mL/g)	3146 (20th percentile of 6 K_{oc} values)	3146 (assumed same to tioxazafen)	428 (estimated for benzamidine using EPI Suite)
	Aerobic soil biotransformation half-life at 20°C(days)	242 (90th percentile confidence on the mean of 4 half-lives)	NA (not observed in soil)	NA (not observed in soil)
	Aerobic aquatic biotransformation half-life at 20°C (days)	6.27 (longer of 2 half-lives in entire system)	Stable	72.23 (longer of 2 half-lives in entire system)
	Anaerobic aquatic biotransformation half-life at 20°C (days)	6.30 (longer of 2 half-lives in entire system)	Stable	84.67 (longer of 2 half-lives in entire system)

[1] The rate of 250 g a.i./ha does not appear on the final product label, but is a conservative estimate for the final maximum label rate of 125 g a.i./ha.

Table 17 Modelled Expected environmental concentrations (EECs) and risk quotients (RQs) for aquatic organisms

Organism	Endpoint[1]					EEC[2] ($mg_{a.i.}/l$)	RQ[3]
Based on the daily maximum concentration in a 80-cm deep water body							
Daphnia sp. Acute Toxicity	1/2	48h- EC50	>	0.6	$mg_{a.i.}/l^{-1}$	0.0015	0.002
Daphnia sp. Chronic (Life-Cycle) Toxicity		21d- NOEC	=	0.0059	$mg_{a.i.}/l^{-1}$	0.0015	0.3
Cold Water Fish (rainbow trout) Toxicity	1/10	96h- LC50	=	0.00911	$mg_{a.i.}/l^{-1}$	0.0015	0.2
Fish, Early Life Cycle Tox. Test (fathead minnow)		33d- NOEC	=	0.0094	$mg_{a.i.}/l^{-1}$	0.0015	0.2
Fresh Water Algae Toxicity	1/2	96h-EbC50	=	0.3557	$mg_{a.i.}/l^{-1}$	0.0015	0.004
Fresh Water diatom Toxicity	1/2	96h- IC50	=	0.06265	$mg_{a.i.}/l^{-1}$	0.0015	0.03
Vascular plants	1/2	7d- IC50	>	0.477	$mg_{a.i.}/l^{-1}$	0.0015	0.003
Midge Larvae		10d- NOEC	=	1.01	$mg_{a.i.}/l^{-1}$	0.00079	0.0008
Based on the daily maximum concentration in a 15-cm deep water body							
Daphnia sp. Acute Toxicity	1/2	48h- EC50	>	0.6	$mg_{a.i.}/l^{-1}$	0.0046	0.008
Daphnia sp. Chronic (Life-Cycle) Toxicity		21d- NOEC	=	0.0059	$mg_{a.i.}/l^{-1}$	0.0046	0.8
Cold Water Fish (rainbow trout) Toxicity	1/10	96h- LC50	=	0.00911	$mg_{a.i.}/l^{-1}$	0.0046	0.5

Fish, Early Life Cycle Tox. Test (fathead minnow)		33d- NOEC	=	0.0094	$mg_{a.i.}/l^{4}$	0.0046	0.5
Fresh Water Algae Toxicity	1/2	96h-EbC50	=	0.3557	$mg_{a.i.}/l^{4}$	0.0046	0.01
Fresh Water diatom Toxicity	1/2	96h- IC50	=	0.06265	$mg_{a.i.}/l^{4}$	0.0046	0.07
Vascular plants	1/2	7d- IC50	>	0.477	$mg_{a.i.}/l^{4}$	0.0046	0.01
Midge Larvae		10d- NOEC	=	1.01	$mg_{a.i.}/l^{5}$	0.00096	0.001

[1] Endpoints used in the acute exposure risk assessment are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
[2] Daily maximum (peak) concentration based on model input presented in Table 9. EECs are for combined residues.
[3] Risk Quotient (RQ) = exposure/toxicity. RQ > 1 would indicate exceedance of LOC (Level Of Concern). Based on an application rate of 250 g a.i./ha that was originally considered but which does not appear on the final product label. The maximum label rate is 125 g a.i./ha, which is lower; water modelling was not redone at the lower rate and RQs are considered conservative
[4] Modeled EEC in the water column for combined residues of tioxazafen (TGAI, 3-thienyl102100, TIOXAZAFEN-iminoamide and benzamidine)
[5] Modeled EEC in sediment pore water for combined residues of tioxazafen (TGAI, 3-thienyl102100, TIOXAZAFEN-iminoamide and benzamidine)

Table 18 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	N/A		Yes
Predominantly anthropogenic[2]	N/A		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes Half-life = 21.7-500 days
	Water	Half-life ≥ 182 days	No Half-life = 4-6 days
	Sediment	Half-life ≥ 365 days	N/A
	Air	Half-life ≥ 2 days or evidence of long range transport	Long-range atmospheric transport is unlikely to occur based on the AOPWIN predicted half-life in air.
Bioaccumulation[4]	Log K_{OW} ≥ 5		4.13
	BCF ≥ 5000		BCFk,g,1 = 2699 - 2833
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).
[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}).

Table 19 Registered Alternatives in Canada for Use as Seed Treatments as of October 2015

Active Ingredient	Crop	Pest
Bacillus firmus strain I-1582	Corn	Suppression of needle, root lesion and root knot nematodes
	Soybean	Suppression of soybean cyst, root lesion and root knot nematodes
Pasteuria nishizawae PN1	Soybean	Suppression of soybean cyst nematode

Table 20 Supported Uses

Supported use claim
Suppression of the following nematodes at the rates of 0.875 mL/1,000 seeds (0.5 mg a.i./seed) for MON 102133 on corn: Root knot nematode (*Meloidogyne* spp.) Cyst nematode (*Heterodera zeae*) Dagger nematode (*Xiphinema* spp.) Root lesion nematode (*Pratylenchus* spp.) Pin nematode (*Paratylenchus* spp.) Spiral nematode (*Helicotylenchus* spp.) Stunt nematode (*Tylenchorhynchus dubius*)
Suppression of the following nematodes at the rates of 0.438 mL/1,000 seeds (0.25 mg a.i./seed) for MON 102133 on soybean: Soybean cyst nematode (*Heterodera glycines*) Root lesion nematode (*Pratylenchus* spp.) Root knot nematode (*Meloidogyne* spp.)
Tank mixtures with the registered Acceleron Seed Treatment Products for crops which they are labelled.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Tioxazafen is a new active ingredient which is concurrently being registered in Canada and the United States. The MRLs proposed for tioxazafen in Canada are the same as corresponding tolerances to be promulgated in the United States, except for livestock commodities, in accordance with Table 1, for which no tolerances are being proposed in the United States.

Once established, the American tolerances for tioxazafen will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[10] listed for tioxazafen in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 compares the MRLs proposed for tioxazafen in Canada with corresponding American tolerances and Codex MRLs. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Meat of cattle, goats, hogs, horses, poultry and sheep	0.02	Not Established	Not Established
Meat byproducts of cattle, goats, hogs, horses, poultry and sheep	0.02	Not Established	Not Established
Fat of cattle, goats, hogs, horses, poultry and sheep	0.02	Not Established	Not Established
Eggs	0.02	Not Established	Not Established
Milk	0.02	Not Established	Not Established

[10] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

2483584	2014, Product Chemistry Data to Support the Registration of MON 102100 Nematicide (Amended from MSL0025779), DACO: 2.0,8.2.1 CBI
2553816	TGAI - Prod Chem AI Amended 2, DACO: 2.0 CBI
2483531	2014, Method Validation for Product Chemistry Study on TIOXAZAFEN Wet Cake (Amended from MSL0025338), DACO: 2.13.1 CBI
2483502	2010, Characterization of DC1822 Reference Standard Lot Syncom 148424, DACO: 2.13.2 CBI
2483560	2012, MON 102100: Vapor Pressure Determination by the Gas Saturation Method, DACO: 2.14.9,8.2.1 CBI
2483509	2011, Determination of Water Solubility of MON 102100 by the Column Elution Method, DACO: 2.14.7,8.2.1 CBI
2553817	TGAI - MON 102100 Solvent Solubility Combined, DACO: 2.14.8 CBI
2483545	2012, TIOXAZAFEN: Determination of n-Octanol/Water Partition Coefficient (Shake Flask Method), DACO: 2.14.11,8.2.1 CBI
2483182	2014, Explosive Properties Testing on a Sample of Tioxazafen (MON 102100), DACO: 3.5.12 CBI
2561634	Product Chemistry Data to support the Registration of MON 102133 as an End-Use Product, DACO: 3.2.2,3.5.14,3.5.5,3.5.8 CBI
2483188	2014, Product Chemistry Data to Support the Registration of MON 102133 as an End-Use Product, DACO: 3.0 CBI
2483497	2014, Analytical Method for the Determination of MON 102100 and its Major Metabolite Benzamindine in Soil, DACO: 8.2.2.1
2483128	2014, Independent Laboratory Validation of an Analytical Method for the Determination of MON 102100 and BEnzamindine in Soil, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,860.1300,860.1340,860.1360,IIA 4.2.6,IIIA 5.3.1,b,d
2483184	2014, Method Validation Study for the Determination of Residues of MON 102100 and Its Degradates in Water Matrices using Liquid Chromatography with Tandem Mass Spectrometry Detectin, DACO: 7.2
2483125	2014, Independent Laboratory Validation Study for the Determination of MON 102100 and Environmental Degradates in Ground, Surface and Drinking Water, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,860.1300,860.1340,860.1360,IIA 4.2.6,IIIA 5.3.1,b,d
2632457	49892201 COA NMR Report RD1805, DACO: 2.11.4 CBI

2.0 Human and Animal Health

2483120	2014, MON 102130: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.6.1
2483131	2014, A 28-Day Oral (Dietary) Toxicity Study of MON 102130 in Sprague Dawley Rats, DACO: 4.6.1
2483132	2014, MON 102133: Acute Oral Toxicity - Up-and-Down Procedure in Rats, DACO: 4.6.1
2483133	2014, MON 102133: Acute Dermal Toxicity in Rats, DACO: 4.6.2
2483134	2014, MON 102133: Acute Inhalation Toxicity in Rats, DACO: 4.6.3
2483135	2014, MON 102133: Primary Eye Irritation in Rabbits, DACO: 4.6.4

2483136	2014, MON 102133: Primary Skin Irritation in Rabbits, DACO: 4.6.5
2483137	2014, MON 102133: Dermal Sensitization Test in Guinea Pigs - Buehler Method, DACO: 4.6.6
2483480	2013, A 90-Day Oral (Diet) Study of MON 102100 in Mice, DACO: 4.3.1
2483481	2013, A 90-Day Oral (Diet) Study of MON 102100 in Rats, DACO: 4.3.1
2483482	2013, A 90-Day Toxicity Study in the Beagle Dog with MON 102100, DACO: 4.3.2
2483486	2014, A dietary Two-Generation Reproductive Toxicity Study of MON 102100 in Rats, DACO: 4.5.1
2483487	2014, A four-Week Dermal Toxicity Study of MON 102100 in Sprague Dawley Rats, DACO: 4.3.5
2483488	2014, The Absorption, Distribution, Metabolism and Excretion of [14C]-MON 102100 following Oral and Intravenous Administration of Rats, DACO: 4.5.9
2483490	2011, Acute Dermal Toxicity Study in Rats, DACO: 4.2.2
2483491	2011, Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.2.1
2483493	2014, An Oral (Gavage) Acute Neurotoxicity Study of MON 102100 in Rats, DACO: 4.5.12
2483494	2012, An Oral (Gavage) Prenatal Developmental Toxicity Study of MON 102100 in Rabbits, DACO: 4.5.3
2483495	2012, An Oral (Gavage) Prenatal Developmental Toxicity Study of MON 102100 in Rats, DACO: 4.5.2
2483499	2014, Bacterial Reverse Mutation Assay, DACO: 4.5.4
2483500	2014, Bacterial Reverse Mutation Assay, DACO: 4.5.4
2483501	2011, Bacterial Reverse Mutation Assay with a Confirmatory Assay with MON 102100, DACO: 4.5.4
2483503	2011, CHO/HPRT Forward Mutation Assay with Duplicate Cultures and a Confirmatory Assay with MON 102100, DACO: 4.5.5
2483504	2011, Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes Treated with MON 102100, DACO: 4.5.6
2483505	2014, An 18-Month Oral (Diet) Carcinogenicity Study of MON 102100 in CD-1 Mice, DACO: 4.4.4
2483508	2011, Dermal Sensitization Study in Guinea Pigs (Buehler Method), DACO: 8.2.2.4, DACO 4.2.6
2483511	2014, In Vivo Micronucleus Assay in Mice, DACO: 4.5.7
2483512	2014, In Vivo Micronucleus Assay in Mice, DACO: 4.5.7
2483513	2011, In Vivo Mouse Bone Marrow Micronucleus Assay with MON 102100, DACO: 4.5.7
2483514	2014, In Vivo Mouse Liver Tumor CAR/PXR Mode-of-Action Study with MON 102100, DACO: 4.8
2483532	2014, A Mode of Action Immunohistochemical Study of Liver Effects of MON 102100 in CD-1 Mice, DACO: 4.8
2483581	2014, PMRA Waiver Request for a 12-Month Dog Study with MON 102100, DACO: 4.3.2
2483582	2011, Primary Eye Irritation Study in Rabbits, DACO: 4.2.4

2483583	2011, Primary Skin Irritation Study in Rabbits, DACO: 4.2.5
2483588	2014, An Evaluation of the Mode of Action and Toxicological Significance of Liver Tumors Observed in a Mouse Oncogenicity Study with MON 102100, DACO: 4.1
2485569	2014, An Evaluation of the Mode of Action and Toxicological Significance of Liver Tumors Observed in a Mouse Oncogenicity Study with TIOXAZAFEN, DACO: 4.1
2493774	Acute Inhalation Toxicity Study in Rats MON 102100, DACO: 4.2.3
2575984	RAT ADME Amended - TIOXAZAFEN TGAI, DACO: 4.5.9
2609719	Seed Dust Off Study, DACO: 5.15
2483121	2014, The In Vivo Percutaneious Absorption of Radiolabelled TIOXAZAFEN in the Concentrate Formulation and Two In-Use Dilutions in the Rat, DACO: 5.8
2483122	2014, The In vitro Percutaneous Absorption of MON 102100 in the Concentrate Formulation and Two In-Use Dilutions Through Rat and Human Skin, DACO: 5.8
1772278	2009, Fluquinconazole and Prochloraz: Determination of operator exposure during cereal seed treatment with Jockey fungicide in Germany, United Kingdom and France, DACO: 5.4
1571553	2007, Determination of Operator Exposure to Imidacloprid During Loading/Sowing of Gaucho Treated Maize Seeds Under Realistic Field Conditions in Germany and Italy, DACO: 5.4
2483115	Analytical Method for the Determination of MON 102100 and Its Major Metabolite Benzamidine in Raw Agricultural and Processed Commodities
2483116	Storage Stability of MON 102100 and Benzamidine in Representative Crop Raw Agricultural Commodities
2483117	Magnitude of MON 102100 Residues in Corn Raw Agricultural Commodities and Processed Fractions Following Seed Treatment Applications
2483118	Magnitude of MON 102100 Residues in Soybean Raw Agricultural Commodities and Processed Fractions Following Seed Treatment Applications 2013 US Trials
2483119	Magnitude of MON 102100 Residues in Cotton Raw Agricultural Commodities and Processed Fractions Following Seed Treatment Applications 2013 US Trials
2483123	Magnitude of MON 102100 Residues in Milk and Tissues of Lactating Dairy Cattle Following Oral Administration
2483126	Independent Laboratory Validation of Analytical Method 115G806A for Determination of Residues of MON 102100 and Benzamidine in Crop Matrices
2483127	Analytical Method for the Determination of MON 102100 Residues in Milk, Meat and Eggs
2483129	Method Validation Study for the Determination of Residues of MON 102100 and Benzamidine in Crop Matrices using Liquid Chromatography with Tandem Mass Spectrometry Detection
2483130	Independent Laboratory Validation of Analytical Method AG-ME-1764 for the Determination of MON 102100 and Benzamidine in Animal Matrices
2483141	Magnitude of MON 102100 Residues in Eggs and Tissues of Laying Hens Following Oral Administration
2483183	Magnitude of MON 102100 Residues in Rotation Crop Raw Agricultural Commodities Following Seed Treatment Application
2483199	A Confined Rotational Crop Study with Two Radiolabeled Forms of ^{14}C-MON 102100 using Radish, Lettuce and Wheat
2483529	Metabolism of [^{14}C]MON 102100 in the Lactating Goat
2483577	Nature of ^{14}C-MON 102100 Residues in Soybean Raw Agricultural Commodities after Application as a Seed Treatment
2483578	Nature of ^{14}C-MON 102100 Residues in Corn Raw Agricultural Commodities after Application as a Seed Treatment
2483579	Nature of ^{14}C-MON 102100 Residues in Cotton Raw Agricultural Commodities after Application as a Seed Treatment
2493775	Metabolism of [^{14}C]MON 102100 in Laying Hens

2553809	Storage Stability of MON 102100, Benzamidine, Benzonitrile and 2-Thenoylglycine in Representative Animal Commodities – Final Report

3.0 Environment

PMRA #	Reference
2483142	2014, Use Description and Scenario for MON 102133 Nematicde Seed Treatment on Corn and Soybean, DACO: 5.2
2485588	2014, MON 102100 (Tioxazafen) Tier II Summaries Environmental Fate, DACO: 8.1
2483197	2014, MON 102100 (Tioxazafen) Tier II Summaires Environmental Fate, DACO: 8.1
2485571	2014, MON 102100 (Tioxazafen) Tier II Summaries Environmental Fate, DACO: 8.1
2483548	2014, MON 102100Tioxazafen Tier II Summaries Environmental Fate, DACO: 8.1
2483510	2014, Environmental Fate and Ecological Risk Assessment for Tioxazefen (MON 102100), DACO: 8.1,9.1
2485586	2014, MON 102100 (Tioxazafen) Tier II Summaries Analytical Methods, DACO: 7.1
2483193	2014, MON 102100 (Tioxazafen) Tier II Summaries - Analytical Methods, DACO: 7.1
2483128	2014, Independent Laboratory Validation of an Analytical Method for the Determination of MON 102100 and BEnzamindine in Soil, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,860.1300,860.1340,860.1360,IIA 4.2.6,IIIA 5.3.1.b,d
2483125	2014, Independent Laboratory Validation Study for the Determination of MON 102100 and Environmental Degradates in Ground, Surface and Drinking Water, DACO: 171 - 4a,171 - 4c,171 - 4m,171-4a-4b,171-4c-4d,7.2.3A,860.1300,860.1340,860.1360,IIA 4.2.6,IIIA 5.3.1.b,d
2483497	2014, Analytical Method for the Determination of MON 102100 and its Major Metabolite Benzamindine in Soil, DACO: 8.2.2.1
2483127	2014, Analytical Method for the Determination of MON 102100 Residues in Milk, Meat and Eggs, DACO: 7.2.1,7.2.2
2483115	2014, Analytical Method for the Determination of MON 102100 and Its Major Metabolite Benzamindine in Raw Agricultural and Processed Commodities, DACO: 7.2.1,7.2.2
2483551	2014, Magnitude of MON 102100 Residues in Eggs and Tissues of Laying Hens Following Oral Administration, DACO: 8.2.2.4
2483498	2014, Analytical Method for the Determination of MON 102100 Residues in Milk, Meat and Eggs, DACO: 8.2.2.4
2483524	2012, MON 102100: Determination of Hydrolysis as a Function of pH, DACO: 8.2.3.2
2483580	2014, Photodegradation of MON 102100 on Soil, DACO: 8.6
2483549	2014, MON 102100: Photodegradation in Water by Direct Photolsys, DACO: 8.2.3.3.2
2483544	2013, Route and Rate of Degradation of [14C] MON 102100 in Four Soils Incubated under Aerobic Conditons, DACO: 8.2.3.4.2
2483515	2014, Kinetics Analysis of Tioxazafen (MON 102100) Laboratory Aerobic Soil Degradation Data using the NAFTA Guidance and PestDF 0.8.4, DACO: 8.2.3.4.2
2483585	2013, Route and Rate of Anaerobic Degradation of [14C] MON 102100 in Four Soils, DACO: 8.2.3.4.4
2483575	2014, NAFTA Kinetics Evaluation of Tioxazafen (MON 102100) Laboratory Anaerobic Soil Degradation Data using PestDF 0.8.4, DACO: 8.2.3.4.4
2483496	2014, Anaerobic Aquatic Metabolism of 14C MON 102100, DACO: 8.2.3.5
2483492	2014, Aerobic Aquatic Metabolism of (14C) MON 102100, DACO: 8.2.3.5
2483517	2013, Determination of Adsorption - Desorption of MON 102100 Using the Batch Equilibrium Method, DACO: 8.2.4.2
2483176	2013, Monsanto TFD Study Rationale - EAD, DACO: 8.3.2
2483138	2014, Terrestrial Field Dissipation of MON 102100 Applied as a Seed Treatment Under Field Conditions at Four Regional North American Locations, DACO: 8.3.2
2483184	2014, Method Validation Study for the Determination of Residues of MON 102100 and Its Degradates in Water Matrices using Liquid Chromatography with Tandem Mass Spectrometry Detectin, DACO: 7.2

2483587	2014, Storage Stability of MON 102100 and Benzamindine in Soil Under Frozen Storage Conditions - Interim Report. DACO: 8.6
2483530	2014, Method Validation Study for the Determination of Residues of MON 102100 and Its Degradates in Water Matrices using Liquid Chromatography with Tandem Mass Spectrometry Detection. DACO: 8.6

Environmental toxicology references

2483139	2014, MON 102133: Effects on the Seedling Emergence and Growth of Non-Target Terresterial Plants (Tier I). DACO: 9.1.9.9
2485570	2014, MON 102100 Tier II Summaries. DACO: 9.1.9.5.1.9.6.1
2483547	2014, mon 102100 Tier II Summaries. DACO: 9.1.9.5.1.9.6.1
2483510	2014, Environmental Fate and Ecological Risk Assessment for Tioxazefen (MON 102100). DACO: 8.1.9.1
2483523	2012, Laboratory Bioassay to Determine the Acute Contact Toxicity of MON 102100 to the Honey Bee (Apis mellifera). DACO: 9.9
2483516	2012, Laboratory BioAssay to Determine the Acute Oral Toxicity of MON 102100 to the Honeybee Apis Mellifera. DACO: 9.9
2483561	2014, MON 102100: Determination of Chronic Toxicity to the Earthworm Eisenia Andrei in an Artificial Soil Substrate. DACO: 9.9
2483522	2013, A 48-Hour Static Acute Toxicity Test with the Cladoceran (Daphnia magna). DACO: 9.3.2
2483562	2014, A 48-Hour Static Acute Toxicity Test with the Cladoceran (Daphnia Magna). DACO: 9.9
2483540	2014, MON 102100: A Flow-through Life-cycle Toxicity Test with the Cladoceran (Daphnia magna). DACO: 9.4.5
2483533	2014, MON 102100: A 10-Day Survival and Growth Toxicity Test with the Midge (Chironomus tentans) using Spiked Sediment. DACO: 9.9
2483484	2013, MON 102100: A 96-Hour Static Acute Toxicity Test with the Saltwater Mysid (Americamysis bahia). DACO: 9.4.2
2483483	2014, MON 102100: A 96-Hour Shell Deposition Test with the Eastern Oyster (Crassostrea virginica). DACO: 9.9
2483541	2013, MON 102100: A flow-through Life-cycle Toxicity Test with the Saltwater Mysid (Americamysis bahia). DACO: 9.4.5
2483540	2014, MON 102100: A Flow-through Life-cycle Toxicity Test with the Cladoceran (Daphnia magna). DACO: 9.4.5
2483534	2014, MON 102100: A 10-Day Survival Toxicity Test with the Marine Amphipod using Spiked Sediment. DACO: 9.9
2485570	2014, MON 102100 Tier II Summaries. DACO: 9.1.9.5.1.9.6.1
2483547	2014, mon 102100 Tier II Summaries. DACO: 9.1.9.5.1.9.6.1
2483567	2014, A 96-Hour Flow-Through Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss). DACO: 9.5.2.1
2483526	2012, A 96-Hour Static-Renewal Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss). DACO: 9.5.2.1
2483485	2014, A 96-Hour Static-Renewal Acute Toxicity Test with the Rainbow Trout (Oncorhynchus mykiss). DACO: 9.9
2483518	2013, A 96-Hour Static-Renewal Acute Toxicity Test with the Bluegill (lepomis macrochirus). DACO: 9.5.2.2
2483527	2012, A 96-Hour Static-Renewal Acute Toxicity Test with the Sheepshead Minnow (Cyprinodon variegatus). DACO: 9.5.2.4
2553814	TGAI Marine Fish Waiver. DACO: 9.5.3.1
2483546	2013, MON 102100: An Early Life-Stage Toxicity Test with the Fathead Minnow (Pimephales promelas). DACO: 9.5.3.1
2483468	2014, 14C-MON 102100: A bioconcentration Test with the Bluegill (Lepomis macrochirus). DACO: 9.9
2483142	2014, Use Description and Scenario for MON 102133 Nematicde Seed Treatment on Corn and Soybean. DACO: 5.2

2485570	2014, MON 102100 Tier II Summaries, DACO: 9.1,9.5.1,9.6.1
2483547	2014, mon 102100 Tier II Summaries, DACO: 9.1,9.5.1,9.6.1
2483519	2012, MON 102100: An Acute Oral Toxicity Study with the Northern Bobwhite, DACO: 9.6.2.1
2483571	2014, MON 102100: Red-winged Blackbird Acute Oral Toxicity Test, DACO: 9.6.2.3
2483521	2012, MON 102100: An Acute Oral Toxicity Study with the Canary (Serinus canaria), DACO: 9.6.2.3
2483520	2011, MON 102100: A Dietary LC50 Study with the Northern Bobwhite, DACO: 9.6.2.4
2483525	2011, MON 102100: A Dietary LC50 Study with the Mallard, DACO: 9.6.2.5
2483543	2013, MON 102100: A Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1
2483542	2013, MON 102100: A Reproduction Study with the Mallard, DACO: 9.6.3.2

4.0 Value

2483144 2014, Efficacy Data to Support the Registration of MON 102100 Nematicide (MON 102133 SC Nematicide Seed Treatment), DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3, 10.3.1,10.3.2, 10.3.3, 10.5.1, 10.5.2, 10.5.3, 10.5.4

B. Additional Information Considered

i) Published Information

1.0 Chemistry

2.0 Human and Animal Health

3.0 Environment

4.0 Environment

Cohen, S.Z., S.M. Creeger, R.F. Carsel and C.G. Enfield. 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. Pages 297-325 In R.F. Krugger and J.N. Seiber, eds., Treatment and Disposal of Pesticide Wastes. ACS Symposium Series No. 259. American Chemical Society, Washington, DC, pp. 297-325.
Gustafson, D.I., 1989. Groundwater ubiquity score: a simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry, v. 8, no. 4, p. 339-357.
United States Environmental Protection Agency, Pest Management Regulatory Agency and California Department of Pesticide Regulation (2012). *White Paper in Support of the Proposed Risk Assessment Process for Bees*. EPA-HQ-OPP-2012-0543-0004. 275pp.
Prosser, Phil and A.D.M. Hart, 2005, Assessing Potential Exposure of Birds to Pesticide-Treated Seeds - Ecotoxicology, Volume 14, Pages 679 to 691, DACO: 9.6.6 (PMRA# 2574060)
Smith, Graham K., 2006, Risks to Birds from Pesticide-treated Seed and the Possible Role of Ultraviolet Reflection in Seed Colour Preferences and Repellent Strategies. A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of Master of Sciences., DACO: 9.6.6 (PMRA# 2574059)